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Dartmouth College and Dartmouth-Hitchcock Medical Center
Committee for the Protection of Human Subjects

CPHS Study Plan for Full Committee Review

Template v. 02/11/2013

Instructions:

The following information in the format provided below is an application for CPHS review. Read through each section and ***respond to each item (even if to indicate NA - not applicable)****. Please also review the CHECKLIST for Full Committee Submission. We have provided some guidance information under each question.*

Please define all acronyms at first use and attach a glossary if more than 3 acronyms are used in this application.

When revising a CPHS reviewed Study Plan for further review, please track the changes. To turn on tracking in this document in Microsoft Word:

1) *Display the forms and reviewing toolbars.*
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Attachments:

Complete and submit Attachment(s) if applicable to the research study.
Attachments may be downloaded from this webpage: http://www.dartmouth.edu/~cphs/tosubmit/forms/StudyPlanAttach

- ☐ *Attachment A: Nonsignificant Risk Devices*
- ☒ *Attachment B: Placebo*
- ☒ *Attachment C: Genetic Research*
- ☒ *Attachment D: Employees and Students*
- ☒ *Attachment E: Illiterate Participants*
- ☐ *Attachment F: Research Involving Children*
- ☒ *Attachment G: Research Involving Individuals With Impaired Decision-Making Capacity (formerly referred to as incompetent)*
- ☐ *Attachment H: Request for Waiver of Participant Consent*
- ☐ *Attachment I: Request for Waiver of Participant Signed Consent Form*
- ☐ *Attachment J: Drugs or Biologics*
- ☐ *Attachment L: International Research*
- ☐ *Attachment M: Pregnant Women, Fetuses and Neonates*

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Local Principal Investigator: **Mary F. Brunette, M.D.**
Department: **Psychiatry**
Study Title: **Cannabis, Schizophrenia and Reward: Self-Medication and Agonist Treatment?**
Funding Source (Sponsor): **National Institute on Drug Abuse (NIDA)**

1. *Abstract.*

Provide an abstract of the proposed research ***in language that can be understood by a non-scientist****. The abstract should summarize the objectives of this project and the procedures to be used, with an emphasis on what will happen to the subjects.* ***(Maximum 250 words)***

Substance use disorders, particularly cannabis and alcohol, are strikingly common in patients with schizophrenia (SCZ) and contribute to its overall morbidity and cost to society. We have proposed a neurobiologic formulation suggesting that cannabis and other substance use in these patients may ameliorate a dysfunction in the brain reward circuit (BRC) (thus serving a "self-medication" function for them), while also worsening their symptoms and course of SCZ.

In this translational research proposal, based on our formulation of the basis of cannabis and other substance use in patients with SCZ, we seek to confirm and expand upon data obtained in our pilot study suggesting that cannabis and the cannabinoid agonist dronabinol, given in low dose to patients with SCZ and co-occurring cannabis use disorder (CUD), will in fact ameliorate the BRC dysregulation in these patients and, thereby, provide evidence in support of the role of cannabis as a "self-medication" agent for them. Moreover, by also testing the full range of effects produced by dronabinol in these patients (effects on brain reward circuitry assessed with task-based fMRI and resting state connectivity (RSC)), as well as on reward responsiveness, mood, craving, cognition, psychiatric and extrapyramidal symptoms), we will provide clues as to whether dronabinol should be tried in low doses as an adjunctive agent (with an antipsychotic medication) to limit cannabis use in patients with SCZ.

This study will involve 8 groups of 25 participants each. Groups 1-3 will have diagnoses of SCZ and CUD (SCZ-CUD); Group 4 will have SCZ only, Groups 5-7 will have CUD only and Group 8 will be healthy control participants. Following screening and baseline neuropsychiatric testing, participants will have two tests days (T1 and T2) that will include task-based fMRI, including assessment of RSC, and measuring a number of other parameters including reward responsiveness, mood, craving, symptoms and cognition. The assessments at T1 will be virtually the same for all groups. At T2 Groups 1-3, and Groups 5-7 will be randomly assigned to one of the following conditions prior to the assessments: receiving 15mg of dronabinol and smoking a placebo marijuana cigarette, receiving two placebo capsules and smoking a real marijuana cigarette, or receiving two placebo capsules and smoking a placebo marijuana cigarette. Group 4 and Group 8 will receive no drug or placebo at T2. Those participants receiving drug will have safety assessments before the drug is administered, after the drug is administered but before leaving the research clinic for the day, and again a week later.

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2. *Objectives & Hypotheses:*

List your research objectives and hypotheses.

In this proposal, we seek to confirm and expand upon our pilot, small "N" pharmacology laboratory investigation of the effects of cannabis and the cannabinoid agonist dronabinol in patients with SCZ-CUD.

Aim 1 of this study will assess the status of the BRC in patients with SCZ-CUD and in healthy controls, as well as in those with SCZ (without CUD) and with CUD (without SCZ):

(1a) To confirm that (i) task-related fMRI activity linked to a monetary brain reward probe; (ii) inter-regional resting state functional connectivity; and (iii) a behavioral measure of reward responsiveness will be decreased in patients with SCZ-CUD as compared to healthy controls; and (1b) to explore these measures in those with SCZ (without CUD) and in those with CUD (without SCZ).

Aim 2 will assess the effects of cannabis and dronabinol on the BRC in patients with SCZ-CUD and in those with CUD (without SCZ): (2a) To confirm whether dysfunctional (i) task-related fMRI activity linked to a monetary brain reward probe, and (ii) inter-regional resting state functional connectivity will be ameliorated when patients with SCZ-CUD smoke a cannabis cigarette, or take a dronabinol pill; (2b) to explore whether a behavioral measure of reward responsiveness will be improved when patients with SCZ-CUD smoke a cannabis cigarette, or take a dronabinol pill; and (2c) to explore the effects of cannabis and dronabinol on these measures in participants with CUD (without SCZ) and to compare the results to those from (2a).

Aim 3 will assess other effects of dronabinol in patients with SCZ-CUD: To determine (3a) whether measures of cannabis craving, mood and negative symptoms will improve; and (3b) whether measures of psychotic symptoms and cognitive deficits will increase (worsen).

By probing BRC dysregulation and testing the effects of smoked cannabis on this dysregulation, this study will help elucidate whether "self-medication" may be an important component of cannabis use in patients with SCZ. Moreover, by further elucidating the physiological effects of dronabinol, this research can lead to development of therapeutic agents, potentially including dronabinol, other cannabinoids or non-cannabinoid agents that may ameliorate a BRC deficiency and thus limit cannabis use in these patients. This is of great importance because, despite the data suggesting that the atypical antipsychotic clozapine (CLOZ) limits cannabis use in patients with SCZ, its side effects discourage many clinicians from using it. Finding new medications, safer than CLOZ, that may be able to limit cannabis use in these patients is thus of great public health importance.

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3. *Introduction:*

a) Explain the background of this project so that we will understand why it is important to perform this research project. b) Summarize previously published data and pilot studies. Be sure to include a discussion of any data that do not support the study hypothesis. If a study similar to the one being proposed has already been completed, explain why the proposed study is necessary. c) For studies designed to compare or evaluate therapies, there should be a statement of the relative advantages or disadvantages of alternative modes of therapy. d) If not obvious, explain why human subjects are necessary. Include references for all published data cited. If a formal protocol for the study exists, page references to the protocol are acceptable.

NOTE: This section is an abridged version of the materials submitted for the grant proposal. For the full background and description of the literature, please see the grant submission.

Schizophrenia (SCZ) is a severe psychiatric disorder occurring in 1% of the population. Patients with SCZ are quite vulnerable to substance use disorders (SUDs); [1 6, 17] It is estimated that, 47% of patients with SCZ have serious problems with alcohol or drug use during their lifetime compared to 16% of the general population. Cannabis use disorder (CUD) occurs commonly in patients with SCZ [18, 19] with lifetime rates three to ten-fold over the lifetime prevalence in the general population.[16] Co-occurring CUD in patients with SCZ has been associated with clinical exacerbations, non-compliance with treatment, poor global functioning, and increased relapse and rehospitalization rates.[1, 8, 16, 18, 21, 23, 29-36]

Basis of cannabis (and other substance) use in SCZ: We have proposed a neurobiologic formulation of the self-medication hypothesis of why person with SCZ have a higher rate of SUDs.[43] Many brain areas that are dysfunctional in SCZ (particularly decreased prefrontal cortex (PFC) activity and hyperactive mesolimbic system)e.g.,[44-46] are part of the dopamine (DA)-mediated "brain reward circuit" (BRC).[47] While cannabis's actions are complex, and may involve many other neural systems, it appears that cannabis, like alcohol, cocaine and other drugs of abuse, produces its reinforcing effects on animal behavior via midbrain DA neurons projecting into the prefrontal cortex and limbic system.[49-58] In patients with SCZ, cannabis and other substance use, which increase DA activity in the PFC,e.g.,[52-54, 59] may also enhance functioning of the dysfunctional BRC by an increase in the neuronally-based "signal detection" of these DA-rich systems.[60, 61]

Thus, the "basis" of the use of these substances in patients with SCZ may be related to the difficulty that these patients have in experiencing "normal" levels of reward from the environment and to the ability of cannabis and other substances of abuse to ameliorate this "reward system" deficit.[43, 47, 62, 63] This proposal gives us the opportunity to gather data supportive of this theory, and, potentially, to create a new medication development strategy for agents that may ameliorate this deficit and thereby limit cannabis use in these patients.

Brain reward circuit dysfunction in SCZ: A number of studies have provided support for a BRC abnormality in SCZ. Structural neuroimaging studies have demonstrated abnormal volumes in several regions of the brain implicated in reward processing.[64, 65] Other studies, including our own, using olfactory and monetary probes of the BRC, measures of resting state functional connectivity, and behavioral assessment of reward responsiveness, have provided further evidence consistent with a BRC dysfunction in patients with SCZ. e.g., [4-8, 66-73]

Functional (f)MRI – monetary incentive delay (MID) studies: A growing body of literature employing fMRI in healthy subjects has provided evidence that monetary probes (e.g., the monetary incentive delay (MID) task) activate several brain regions linked to the processing of reward.[74-79] A number of fMRI studies [4-7, 71, 72] have found that patients with SCZ, with no

history of substance use disorder (SUD), have a deficit of response within the nucleus accumbens during anticipation of monetary reward, despite an ability to perform the task normally. Moreover, our group has also demonstrated a BRC deficit in the nucleus accumbens of patients with SCZ and CUD. The proposed study will allow us to confirm and extend this finding.

Resting state functional connectivity (RSC) studies: RSC analysis uses estimates of inter-regional synchrony to detect neural circuit abnormalities without the complexities sometimes encountered when using task-based functional analysis methods, e.g., such as differential performance levels.[85, 86] Using RSC in normal controls, Di Martino and colleagues[91] identified cortical-striatal circuits, including one consistent with the BRC that they termed the "reward-related motivational circuit" (comprised of the nucleus accumbens, anterior cingulate cortex and lateral orbitofrontal cortex). To our knowledge, our pilot data (see below) are the first to suggest that RSC can in fact delineate decreased inter-regional synchronization in the BRC in patients with SCZ-CUD. The proposed study will allow us to confirm and expand upon these pilot data.

Probabilistic Reward Task studies: A number of studies have used a behavioral measure of reward responsiveness, the Probabilistic Reward Task,[93] to probe the integrity of the BRC in SCZ. Specifically, the task measures the extent to which a participant biases their responding toward more rewarded versus less rewarded stimuli, consistent with the view that response frequency is increased towards reinforcers.[94] On this measure, patients with SCZ show improved reward responsiveness following treatment with varenicline,[95] and our pilot data, as well as AhnAllen et al.,[73] suggest the ability of this measure to serve as a behavioral probe of the BRC deficit in patients with SCZ. We note that although one study[97] did not observe abnormal response bias on the task in patients with SCZ, this study did not regulate the use of nicotine (which is known to improve performance on the task).[98] By contrast, our study regulated nicotine use, and our proposed study will as well.

Effects of cannabis or THC on BRC in SCZ: There has been limited investigation of the effects of cannabis on neural activity in SCZ. In one study, in which a patient with SCZ secretively smoked cannabis between two SPECT scan sessions, striatal DA D2 receptor binding significantly decreased after cannabis use, suggesting increased synaptic DA activity.[99-102] PET studies involving acute delta-9-tetrahydrocannabinol (THC) administration in non-SCZ cannabis users have observed increased blood flow in frontal, cerebellar, anterior cingulate, and other paralimbic regions during rest,[103-107] with, however, conflicting data about release of striatal DA.[108-110] Our pilot data (below) are the first to suggest that cannabis and the cannabinoid agonist dronabinol may increase activation of and connectivity within the BRC in patients with SCZ-CUD, and thus ameliorate their BRC dysfunction. This proposal will allow us to expand upon these pilot data.

Treatment of patients with SCZ and CUD: The treatment of SCZ involves the use of antipsychotic drugs, which appear to be of limited value in controlling substance use. [111] By contrast, a number of studies, including several from our group, suggest that the atypical antipsychotic CLOZ may be helpful in limiting cannabis and other substance abuse in patients with SCZ.[112-122] Moreover, we completed a randomized study of CLOZ vs. other antipsychotics in 35 patients with SCZ and CUD, which indicated that patients treated with CLOZ had fewer days of cannabis use compared to those treated with other agents ($p<.06$).[123] Regarding other atypical antipsychotic medications, the available data are somewhat mixed and not overly promising.[111, 124-135] Thus, CLOZ remains the only antipsychotic where there is consistent evidence of a substantive decrease in cannabis and other substance use. However, given CLOZ's side effects, which limit its clinical use, a search for other agents that are at least as effective as CLOZ for limiting cannabis use, but are safer, is appropriate. This proposal may help facilitate that search.

Cannabis and dronabinol – testing the BRC hypothesis: As described above, we have hypothesized that patients with SCZ have BRC dysregulation underpinning their cannabis use, and that cannabis use in these patients serves to "self-medicate" this BRC abnormality. To build upon the supportive data from our pilot study, in this protocol we will assess measures of BRC functioning in patients with SCZ-CUD (and in those with CUD alone) both during cannabis abstinence and after smoking a cannabis cigarette.

Dronabinol – a potential treatment? Our formulation of the action of CLOZ suggests it is able to decrease cannabis use in patients with SCZ because of a putative ability to ameliorate a BRC deficit in these patients. Our pilot data further suggest that the THC agonist dronabinol, if given at low dose, may have a similar effect. We propose to confirm and extend, in a laboratory setting, the data from our small "N", pilot study regarding the effects of low doses of dronabinol on: (1) activation of BRC during an fMRI monetary incentive delay task and connectivity within BRC during rest; (2) reward responsiveness; (3) craving for cannabis, as well as the "high" and "liking" it produces; (4) mood; (5) cognition; (6) psychiatric symptoms; and (7) extrapyramidal (EPS) side effects of medication. If dronabinol can be clearly demonstrated to improve BRC functioning and, potentially, measures of mood, craving or negative symptoms, without worsening cognition or psychotic symptoms, it would be appropriate to determine in a prospective trial whether it would be a useful adjunctive treatment (given with an antipsychotic medication) for patients with SCZ and co-occurring CUD.

OVERVIEW OF PROPOSED STUDY

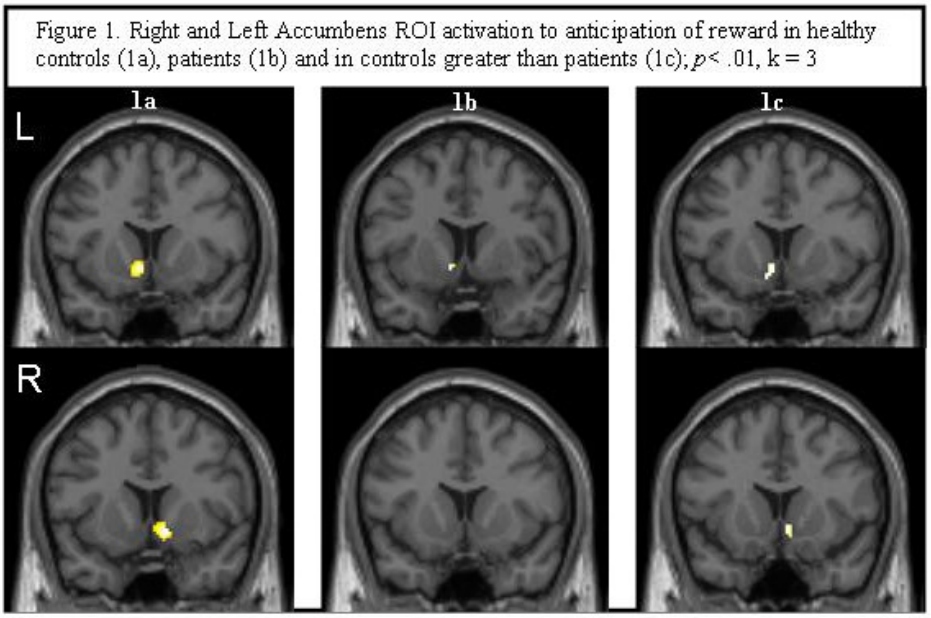
In this translational research proposal, based on our formulation of the basis of cannabis and other substance use in patients with SCZ, we seek to confirm and expand upon data obtained in our pilot study suggesting that cannabis and the cannabinoid agonist dronabinol, given in low dose to patients with SCZ and co-occurring CUD, will in fact ameliorate the BRC dysregulation in these patients and, thereby, provide evidence in support of the role of

cannabis as a "self-medication" agent for them. Moreover, by also testing the full range of effects produced by dronabinol in these patients (effects on brain reward circuitry assessed with task-based fMRI and RSC), as well as on reward responsiveness, mood, craving, cognition, psychiatric and extrapyramidal symptoms), we will provide clues as to whether dronabinol should be tried in low doses as an adjunctive agent (with an antipsychotic medication) to limit cannabis use in patients with SCZ.

This innovative study proposes to include control groups with SCZ (without CUD) and CUD (without SCZ) in the study will allow us to begin to tease apart the differential influences of SCZ and CUD on BRC dysfunction. Moreover, by further elucidating the effects of cannabis and dronabinol on the BRC in patients with SCZ-CUD (as well as in those with CUD alone), this innovative translational research project may also lead to other agents that ameliorate dysregulated brain reward circuitry in patients with SCZ and thus may also be able to decrease their cannabis use. This is of importance since the only medication that has been shown to limit cannabis use in these patients – CLOZ – is not able to be used routinely in these patients due to its severe side effects.

Preliminary Studies:
The PI and colleagues have focused on issues related to SCZ and co-occurring alcohol and/or CUD and on alcohol use disorder without SCZ over the past 12 years, with studies funded by NIH and industry. They have addressed the effect of CLOZ and related compounds on alcohol drinking in rodents; the development of an animal model of SCZ and alcohol abuse; clinical trials of medications for SCZ and alcohol or cannabis use disorders; medication trials for alcohol use disorder; and neuroimaging studies of the BRC in patients with SCZ and co-occurring CUD. Here we briefly describe those studies most relevant to this application.

FMRI (MID) assessment of BRC in patients with SCZ and CUD: Under funding from NIDA, we assessed BRC functioning in 14 patients with SCZ and CUD and in 10 normal controls, using a monetary incentive delay (MID) task linked to fMRI, similar to the technique reported by Knutson et al.[83, 153] Results are presented in Figure 1 for the anticipation of winning a reward relative to no reward using a nucleus accumbens ROI. Significant ($p.<0.01$) activation in the healthy control group is seen in the nucleus accumbens bilaterally (1a), but very little activation is seen in the patient group (1b), and comparison of the groups shows decreased accumbens activation bilaterally in the patient group relative to the controls (1c). This finding is consistent with prior fMRI studies of reward processing in healthy adults and patients with SCZ.[4-8]



Cannabis or dronabinol in patients with SCZ and CUD: We obtained pilot data in 15 subjects with SCZ and CUD. We built an MRI-compatible vented hookah-like device and hood to allow for cannabis smoking in the scanner room. Using this device, we determined that smoking two-thirds of a 3.6% cannabis cigarette (utilizing the Foltin method[155]) produces a moderate "high" in patients who abstained from cannabis for at least 7 days, but without producing untoward psychosis. We also determined that a 15 mg dronabinol pill, in contrast to a 5 mg or a 10 mg pill, produces a moderate level of "liking" in patients who had abstained from using cannabis for at least 7 days, but does not increase psychotic symptomatology. THC plasma levels from the 3.6% (THC) cannabis cigarette peaked shortly after smoking. This confirmed the decision for the dose of the dronabinol pill and (THC) cannabis cigarette; and provided data to indicate the proper timing of smoking a cannabis cigarette to ensure an adequate THC plasma level during our pilot scanning protocol. We also gathered pilot imaging and reward responsiveness data from 12 subjects with SCZ-CUD, and 12 normal controls, utilizing a protocol similar to that proposed below. Baseline data (T1, obtained after at least 7 days of cannabis abstinence and before they smoked a cannabis cigarette or took a dronabinol pill) revealed that patients with SCZ-CUD have a deficit in BRC functioning using the MID paradigm, similar to that noted in Figure 1.

Patients also showed significantly ($p < 0.05$, FDR corrected) decreased resting state functional connectivity of the bilateral nucleus accumbens seed regions[91] with ventral anterior cingulate cortex (ACC), orbital frontal cortex (OFC), anterior PFC, parahippocampal cortex and insular cortex, as compared to control subjects. (By contrast, hyperconnectivity was detected in the default mode network (DMN), as we have reported previously in patients with SCZ [without CUD])[90] Moreover, using a behavioral measure, the Probabilistic Reward Task,[93] we observed reduced baseline reward responsiveness in the patients compared to the normal controls, as indicated by the greater response bias in the control group than the patient group.
One week after baseline testing (T1), while still abstinent from cannabis, 6 patients received a

cannabis cigarette and 6 received a dronabinol pill. During anticipation of reward in the MID task, patients who smoked cannabis showed significantly increased fMRI activation relative to baseline in several regions of the BRC including the ventral tegmental area and the medial prefrontal cortex, while those given dronabinol showed increased activation in BRC regions such as the caudate and the medial prefrontal cortex. Patients in both the cannabis and dronabinol groups demonstrated increased RSC ($p < 0.05$, FDR corrected) between the nucleus accumbens and the OFC, ventral ACC, anterior PFC and parahippocampal cortex (Fig. 2b and 2c). (By contrast, hyperconnectivity in the DMN decreased with both cannabis and dronabinol.) Moreover, the observed increases in RSC of the BRC correlated with plasma THC levels taken immediately prior to the resting scan. Together, these pilot data provide preliminary support for our hypothesis that patients with SCZ may use cannabis in an attempt to normalize dysregulated BRC, and, moreover, that dronabinol, used in low doses, may have similar effects without producing an increase in psychosis.

4. *Design, procedures, materials and methods:*

Use a level of detail similar to what would be used when submitting an article for publication in a peer reviewed journal. Explain the study procedures, data collection, and analysis process. Please define terms and explain concepts which might be confusing to reviewers who are not expert in the area of the study. If a formal protocol for the study exists, page references to the protocol are acceptable.

Overview: This study is an investigation of the effects of cannabis and of the cannabinoid agonist, dronabinol, in "dual diagnosis" participants with SCZ and co-occurring CUD, at the Dartmouth-Hitchcock Medical Center (DHMC) the University of Vermont (UVM) and the White River Junction Veterans Administration Medical Center (WRJ VAMC). The study, involving a total of 200 participants (out of 400 recruited), will include 8 participant groups (N=25/group):

Groups 1, 2 and 3 – participants with SCZ-CUD
Group 4 – control participants with SCZ (without CUD)
Groups 5, 6 and 7 -- control participants with CUD (without SCZ)
Group 8 -- healthy control participants.

Participants will be studied using the MID task and Paced Motor task linked to fMRI, resting state functional connectivity, and the Probabilistic Reward Task (a measure of reward responsiveness). Additional assessments will include measures of psychiatric symptoms, craving for cannabis, mood, "high", "liking", cognitive measures, extrapyramidal (EPS) side effects of antipsychotic medications, and plasma levels of THC.

Following medical center guidelines, participants will be asked about symptoms of COVID-19, exposure to someone with COVID-19 and travel, and will also be assessed for fever; visits will not occur if they have symptoms or recent exposure. Participants will be required to wear a mask covering their mouth and nose, and research staff will wear protective equipment per medical center guidelines during study visits.

After completing the informed consent process, participants will be screened for study eligibility. The Baseline Neuropsychiatric Testing Visit will occur once participants have achieved 7 days of abstinence from cannabis and other substances. Once participants have achieved 14 days of abstinence, they will be assessed with the fMRI protocol and other measures twice -- at Time 1 (T1) and Time 2 (T2), each separated by a target duration of 7 days (minimum 2 days with no set maximum time interval between scan days) with continued criteria of 14 days of abstinence before T2). At T1, the assessment will occur without any intervention. At T2, the assessment will occur after administration of a double-blinded cannabis cigarette and a placebo pill for participants in Group 1; a double-blinded placebo cigarette and a dronabinol pill for participants in Group 2; and a double-blinded placebo pill and a placebo cigarette to participants in Group 3. Participants in control Groups 4 and 8 will receive no intervention at Time 2. Participants in control Groups 5, 6 and 7 (CUD without SCZ) will be studied in the same fashion as those in Groups 1, 2 and 3, i.e., with an intervention at T2.

Protocol: Screening assessments (including medical history and physical assessment) will confirm inclusion and exclusion criteria. If participants, who are otherwise eligible, require more time to meet certain eligibility criteria (e.g., additional time to meet one month on a stable dose of antipsychotic), they may proceed to the Abstinence Period and Baseline Neuropsychiatric Assessment Visit, however, participants must meet all applicable eligibility criteria before proceeding to the T1 scan day. Patient eligibility will be reviewed by a study physician prior to the T1 Scan Day.

Abstinence Period: All study participants will be asked to refrain from any cannabis, alcohol, other substance use (except nicotine and caffeine) for a period of 14 days after the screening assessments until the day of T1, described below. (Note: If the study proves not to be feasible with a period of 14 days of abstinence, the PI will decrease the interval to 7 days as in the previous study.) Participants who are in the groups that use marijuana will be told that it can take days or weeks for THC to no longer be detected in the body, instructed about the schedule of assessments to assess/reinforce their abstinence, and educated about cannabis withdrawal. Participants will be assessed for cannabis withdrawal at each visit.) A Timeline Followback (TLFB) interview and urine/breath tests (to confirm substance abstinence) will be obtained approximately 6 times (up to 3x per week with a minimum of once per week) during this period and approximately 3 times per week with a minimum of once per week during the period betweenT1 and T2 for participants with a CUD. (See details below for Groups 4 and 8 who do not have any history of a substance use disorder) Those whose tests indicate abstinence will receive a $30 credit to encourage continued abstinence. Study participants and control participants will only progress to the Scan Days of the study if they achieve 14 days of substance abstinence and will only progress to the Baseline Neuropsychiatric Assessments if they achieve 7 days of substance abstinence.

The criteria for determining abstinence will be as follows:

- For alcohol and substances other than cannabis and synthetic cannabinoids, if the person reports being abstinent on the TLFB since last assessment and tests negative for the substance, they will be considered abstinent.
- For cannabis, the following two criteria must be met for the person to be consider abstinent:
    - The person reports being abstinent on the TLFB since last assessment and;
    - The dipstick test for cannabis is negative or if the dipstick test is positive, results of quantitative testing at the reference lab indicate abstinence (e.g. downward trend in THC level and/or low levels of THC in the participant's urine.
- For synthetic cannabinoids (aka K2/Spice) the following procedure will be followed.
    1. If patients deny ever using synthetic cannabinoids in the past year at the Screening Visit and this is confirmed by the reference lab, then abstinence for synthetic cannabinoids will consist of the participant's self-report on TLFB. The only additional specimens to be sent to the reference lab are those at the Baseline Neuropsych Testing and on the two scan days. Participants will be paid based solely on their report on the TLFB and no payments to participants for abstinence will be held pending completion of this testing (see below).
    2. If patients report using synthetic cannabinoids in the past year at the Screening Visit, then abstinence for synthetic cannabinoids will consist of the participant's self-report on TLFB and sending a urine specimen from each visit to the reference lab for testing. Participants will be paid based on both their report on the TLFB and the result from the reference lab.
    3. If patient denies use of synthetic cannabinoids at screening, but tests positive for these drugs or later admits to use, the procedure outlined in #2 (above) will be followed.

There is a delay of 4-7 days in obtaining quantitative results from the reference lab. Payments for abstinence will not occur until there is enough information to state that the participant has been abstinent. Baseline neuropsych testing, will be conducted while reference lab results are pending as long as all other assessments indicate that the patient has been abstinent. At the T1 and T2 scans the urine must test negative on site in order to proceed with scanning.

The criteria for determining abstinence for Study Group 8 (Healthy Controls) will be based on the participant's report of abstinence from alcohol and drugs and confirmation by a negative test on the breathalyzer and urine dipstick test for cannabis and other drugs. Participants in Group 8 will not be required to have additional visits 3x per week to encourage abstinence. The criteria for determining abstinence for Study Group 4 (Schizophrenia Only) will be the same with the exception that staff will attempt to contact participants once during each week to assess and encourage further abstinence.

Any substance use other than cannabis by a participant who is abstinent from cannabis shall be reviewed with Dr. Brunette. Use that is likely to affect the risks to participants or the results of assessments will result in postponement of T1 and T2 Days. An isolated instance of using a substance a few days prior to testing is unlikely to affect the study results or risk; whereas continued regular use of a substance could produce such an effect.

Baseline Neuropsychiatric Testing: After a minimum of 7 days of abstinence, patients will come into the laboratory or their local clinic as applicable for the Baseline Neuropsychiatric Assessments. This testing will include extrapyramidal side effect (EPS) assessment and cognitive testing. If necessary, it may be possible to conduct some or all of this testing during the Scan Days.
Based on participants' prior exposure to MRI scanning, research staff will introduce participants to the scanner procedures, show them the scanner, and teach them relaxation techniques (if they are concerned about being anxious in the scanner.) If the scanner is not available for this purpose during the Baseline Visit, this will be done at the first MRI Visit.

Scan Days - Day of T1: T1 will occur as soon as possible after at least 14 days of abstinence. Please note that the exact schedule may need to be modified due to unforeseen events, such as participants arriving late or encountering some form of difficulty and participant schedules. Participants who are caffeinated beverage drinkers will be given a caffeinated beverage (coffee, tea, soda, etc) in order to prevent caffeine withdrawal which may affect the brain reward circuit. (The exact schedule of caffeine, nicotine and food intake may need to be varied to account for changes in the schedule.) All patients with SCZ will be asked to take their usual morning antipsychotic medication at approximately the same time as usual. When participants arrive at the hospital for their scan, they will undergo urine/breathalyzer/pregnancy testing and they will be given breakfast (or similar meal as applicable). Assuming confirmation of continued abstinence (and non-pregnant status), an intravenous line will be inserted with a heparin lock to allow for blood draws (to make the conditions similar to T2, in which participants in Groups 1, 2, and 3, and in Groups 5, 6, and 7 are given an intervention (dronabinol or a cannabis cigarette) and have several tubes of blood drawn.) Lidocaine may be applied to or injected into the skin prior to inserting the needle for patient comfort. At T1, a single specimen of blood will be drawn from all groups to assess participant THC level. Also, if the participant uses nicotine products they will be asked to use these nicotine products at specified times and blood will be drawn to assess the person's nicotine level. All participants will be asked to rate their mood. Participants with CUD will be asked to rate their craving, liking and high. Staff will take vital signs. Participants with SCZ will be rated with brief assessments for psychotic and negative symptoms, as well as EPS. At intervals throughout the day, they will again rate their high, liking, mood and craving and their vital signs will be assessed. The fMRI protocol is described below. After leaving the scanner, they will rate their high, liking, mood and craving, their vital signs will be taken and they will be assessed for reward responsiveness, rated for psychotic and negative symptoms, as well as EPS, and brief

cognitive testing (see below) will be performed. A schedule of events explaining which tasks will occur with the various groups is attached.

Participants will be instructed to continue to maintain abstinence and will be given an appointment for the next fMRI testing day, as well as for a visit at their local clinic to give a urine drug screen and breathalyzer (if appropriate). To assess for possible adverse events from the procedures, participants in all groups will be contacted the day after discharge from the laboratory.

Note: If participants need an abbreviated schedule for Scan 1 to work around schedule constraints (work, school, childcare), we will accommodate this by eliminating time gaps between the events of the day. The study team may also move the start of the day earlier or later to accommodate participant schedules.

Day of T2 (to occur approximately 7 days after T1):

Groups 1, 2 and 3 (dual diagnosis participants): Prior to receiving the study capsules and study cigarette all participants in these groups will be assessed by a study physician to determine that they are stable and can safely continue with the study visit. Participants in Group 1 will receive 2 (double-blinded) placebo capsules and a 3.6%* cannabis cigarette; participants in Group 2 will receive two 7.5 mg dronabinol capsules and a placebo cigarette; and participants in Group 3 will receive two placebo capsules and a placebo cigarette. Research assessment staff will be blind to group assignment. The pill and cigarette will be dispensed at times to facilitate peak THC levels during the scans. All other procedures outlined for the T1 testing period, above, will apply. When smoking the cannabis or placebo cigarette, participants will be instructed in the use of the "Foltin" method:[155] "light the cigarette" (approximately 30 seconds); "prepare to smoke" (approximately 5 seconds); "inhale" (approximately 5 seconds); "hold smoke in lungs" (approximately 10 seconds); and "exhale". They will smoke 3 puffs in this manner, or until they have consumed 2/3 of the cannabis cigarette.[14] Blood draws will occur for assessment of THC at set intervals. If the participant uses nicotine products blood will also be drawn to assess the person's nicotine level.

* We will obtain our cannabis cigarettes (and placebo cigarettes) from NIDA based on their available stock. We will aim for approximately 3.6% THC cigarettes for the active THC cigarettes.

Groups 4 and 8 (control participants with SCZ without CUD, and normal controls): These control participants will follow the same protocol as participants in Groups 1, 2 and 3, except that they will not be given capsules or a cannabis cigarette at T2. Although they will have an intravenous line inserted, but only a single blood specimen drawn to confirm abstinence from THC. If the participant uses nicotine products, blood will also be drawn to assess the person's nicotine level. Control participants with SCZ (Group 4) who are regular cigarette smokers

will smoke a cigarette prior to the fMRI protocol as described for Groups 1, 2 and 3. Normal control participants (Group 8) will not be cigarette smokers.

Groups 5, 6 and 7 (control participants with CUD without SCZ): These control participants will follow the same protocol as participants in Groups 1, 2 and 3, including the intervention at T2. Those who regularly use nicotine products will use these nicotine products prior to the fMRI protocol and have blood drawn to assess the person's nicotine level as described for patients in Groups 1, 2 and 3.

At the end of the T2 testing sessions, participants in Groups 1 - 3 and 5 - 7 will be assessed by an MD to ensure that they are able to safely leave the laboratory. Lorazepam and haloperidol will be available in case of untoward reactions to dronabinol or cannabis. All scans occur at a medical center thus treatment will be available as needed based on the presenting medical issue. If participants are deemed unstable clinically, they will be observed further until stable or they will be admitted overnight. To monitor for reactions from the drug or procedures, all groups will be contacted the day following T2 and again approximately one week after T2 for a brief check-in. At the one-week call, Group 1-3 participants will be assessed for cannabis and other substance use (TLFB), psychiatric symptoms (using items from the PANSS Positive Scale) and adverse events. Group 5-7 participants will be assessed for cannabis and other substance use (TLFB), and adverse events. If participants are having clinical difficulties, we will ensure that appropriate treatment is initiated. Participants will be contacted approximately 30 days after the end of the protocol to assess for any changes in adverse events.

We may repeat assessments in cases of unplanned technical difficulties or need to further evaluate or monitor participants and would compensate accordingly.

If we experience technical difficulties with the MRI scanner we may ask the participant to return to repeat appropriate study measures and the MRI scan and we would compensate accordingly.

In order to provide flexibility to study participants who may not be able to attend an appointment on the exact date of the protocol, we will allow some flexibility for scheduling appointments, but the window between Scan Days will be at least 2 days. If a participant misses a study Scan day due to illness or other unforeseen factors, s/he will be rescheduled as soon as possible. Because this population is typically unstable and often misses appointments, we expect scheduling difficulties and missed appointments to occur frequently. Research staff will work with participants to support their attendance. The maximum allowed time between the Screening Visit and the T1 Scan is 10 weeks. If a study participant goes beyond this time frame, then he or she will need to be reconsented. Also, any assessments required to establish eligibility and medical stability for the study will need to be repeated. Tasks for which the PI

believes there is no scientifically valid reason to repeat (e.g., WRAT or Baseline Neuropsychiatric Testing) will not be repeated.

Structural and Functional MRI Protocol:
Implementation: The neuroimaging protocol will be carried out at DHMC and UVM, overseen by our lead neuropsychologist. Our laboratory includes a "smoking hood", which allows for cannabis smoking in the scanner room and venting of smoke outside the laboratory. Within the scanner, participants will undergo a resting state scan, and the MID task, Paced Motor task, Aterial Spin Labeling (ASL), and (only at T1) a structural scan.

FMRI Imaging Parameters: MRI is a well-known noninvasive procedure typically used to image neuroanatomical structures. This is accomplished via the use of a high magnetic field and high frequency radio waves passing through the brain.

RSC and Data Processing: Participants will be asked to lie in the scanner for approximately 8 minutes with eyes open, maintaining fixation,[192] trying to not think of anything in particular, and not fall asleep.[193] It has been recently demonstrated that artifacts from participant motion result in substantial and structured changes in RSC data ***despite*** standard compensatory spatial registration and regression of motion estimates from the data.[194-196] Quality Assurance (QA) procedures will be implemented to detect outliers in global signal intensity and motion time series with artifact mitigation software, with the identified outliers subsequently treated as confounds in the first level Generalized Linear Model (GLM.) Physiological sources of noise will be estimated and also treated as confounds. Anatomical volumes will be segmented into grey matter, white matter, and cerebrospinal fluid (CSF) areas. The time series characterizing estimated participant motion, as well as the blood oxygen level dependent (BOLD) time series within the participant-specific white matter mask and CSF mask, will be used as temporal covariates and removed from the BOLD functional data using linear regression, and the resulting residual BOLD time series will be band-pass filtered. Correlation maps will be produced by extracting the residual BOLD time course from seed regions, and computing correlation coefficients between that time course and the time course of all other voxels. Correlation coefficients will be converted to normally distributed scores to allow for second-level GLM analyses. We will assess RSC of the BRC using anatomically defined seed regions of interest (ROIs) (e.g., bilateral nucleus accumbens) defined by the literature.[4, 91]

MID Task: Participants will complete an event-related fMRI MID task similar to that used in numerous studies of healthy participants,[83, 166, 198] patients with SCZ[4-8, 71, 72] and in our preliminary studies. Prior to scanning, instructions and the opportunity for a practice trial will be provided. In the scanner, visual stimuli will be presented electronically (e.g. through an MR-compatible goggle system) and response recorded electronically through an MR-compatible button response system. During the task, the participant is shown cues that indicate how much money can be won or lost on a given trial. This is followed by a fixation point of variable interval (estimated range of delay is 3000-7500ms) and then a square target

stimulus. Following the disappearance of the target, feedback is provided as to the amount of money won for correct responses to the target (responding while target is displayed). An incorrect response is also indicated. Feedback is followed by a variable inter-trial interval (ITI). Each cue is presented an equal number of times in a pseudo-randomized order. Following completion of the session, participants will be told that they won $35 during the task (the amount is fixed at $35 to ensure that all participants receive the same amount irrespective of performance capacity).

Pulsed Arterial Spin Labeling (PASL): Since it is not known if cannabis or dronabinol will induce neurovascular changes, we will use PASL [203-209] to characterize resting regional cerebral blood flow (CBF) during each scan session.[210-212] ASL methods measure CBF by using water in arterial blood as an endogenous tracer.[206, 213] PASL, which alternates control and labeling scans that are then compared to quantify perfusion,[214, 215] will be implemented.[216] Derived perfusion images will be coregistered to the fMRI and anatomic scans and analyzed by tissue compartment and project-specific ROIs. Masks derived from segmented anatomic maps will be used to estimate global and local gray matter and white matter perfusion values. Perfusion will also be determined for the same ROIs targeted in the fMRI experiments.

fMRI Paced Motor Task (PMT): Participants will complete a visually-triggered sequential finger movement fMRI task in which periods of finger movement alternate with rest for a total of 8 minutes.

Structural MRI Imaging Parameters: Structural scans will be acquired during the baseline scan session only. We will also acquire survey images as a screen for focal lesions. T1-weighted anatomic reference images will be acquired in the same planes and thickness during each scan session. The magnet's repositioning system will be used to ensure comparable head positioning across the scan sessions.

Eye Camera: We will use an MRI-compatible camera with integrated LED infrared light (MRC Systems, Germany; model 12M-I) that can be used inside the bore of the scanner. This will allow us to monitor and record participant's eyes to determine whether they are keeping them open/closed per instructions during the scan session. The camera is based on a single light-emitting-diode (LED) which is embedded in the titanium housing and emits diffuse light.

GENETIC TESTING

Each participant will be asked whether he/she would be willing to donate a small amount of blood for the relation of genetic markers for mental health, substance abuse, and brain function. There is a separate consent form for this part of the study. DNA will be extracted from this blood sample and stored in a freezer at DHMC, labeled only with the subject's ID number, and the date of blood draw. There are several methods that may be used to genotype the study population. We will choose the most cost-effective, accurate and scientifically

appropriate methods at the time of processing. Options will include standard or custom single SNP and genome-wide arrays, as well as intermediate density sampling such as the custom 3300-SNP microarray designed by the PI and colleagues at Dartmouth. Genotyping will be carried out within Dartmouth and/or other qualified genotyping facilities, such as Illumina or Affymetrics, as appropriate depending on the assay conducted. If blood is sent to a facility such as Illumina or Affymetrics for testing, unused portions of the samples will be destroyed or returned to Dartmouth. The samples will be stored in de-identified form at Dartmouth until all the studies and assays associated with the research program have been completed. Analyses will be conducted at the single SNP level and at the level of complex gene-gene interactions and multivariate biological pathways in conjunction with the Computational Genetics Lab at Dartmouth.

5. *Inclusion/Exclusion Criteria:*

Please provide detailed description of inclusion and exclusion criteria. If a formal protocol for the study exists, page references to the protocol are acceptable.

Inclusion Criteria:

Groups 1-3 - Participants with SCZ-CUD

1. Ages 18 – 55 years old, inclusive
2. Diagnosis of schizophrenia or schizoaffective disorder as confirmed with the Structured Clinical Interview for the DSM (SCID)
3. Diagnosis of cannabis abuse or dependence as confirmed by the SCID
4. Use of cannabis within the month prior to screening based on the TLFB
5. Willing to remain abstinent for the 7 days before the baseline assessments and 14 days before the two scan days. Note: If the 14 day period of abstinence is too great a barrier for participants, the PI may decrease the amount to 7 days.
6. Psychiatrically stable as indicated by being treated as an outpatient for the past month as determined by a study physician's review
7. Currently stable in treatment (either on an antipsychotic or not) for the past month as determined by a study physician's review
8. Not seeking treatment for their CUD.

Group 4 - Control participants with SCZ

1. Ages 18 – 55 years old, inclusive
2. Diagnosis of schizophrenia or schizoaffective disorder as confirmed with the SCID
3. Willing to remain abstinent for the 7 days before the baseline assessments and for 14 days before the two scan days. Note: If the 14 day period of abstinence is reduced for the groups with a CUD, it will be reduced for Group 4 also.
4. Psychiatrically stable as indicated by being treated as an outpatient for the past month, as determined by a study physician's review

5. Currently stable in treatment (either on an antipsychotic or not)for the past month as determined by a study physician's review

Groups 5-7 - Control participants with CUD

1. Ages 18 – 55 years old, inclusive
2. Diagnosis of cannabis abuse or dependence as confirmed by the SCID
3. Use of cannabis within the month prior to screening based on the TLFB
4. Willing to remain abstinent for 7 days before the baseline assessments and 14 days before the two scan days. Note: If the 14 day period of abstinence is too great a barrier for participants, the PI may decrease the amount to 7 days.
5. Not seeking treatment for their CUD.

Group 8 – Healthy control participants

1. Ages 18 – 55 years old, inclusive
2. Willing to remain abstinent for the 7 days before the baseline assessments and 14 days before the two scan days. Note: If the 14 day period of abstinence is reduced for the groups with a CUD, it will be reduced for Group 8 also.

<u>Exclusion criteria:</u>

Groups 1-3 with SCZ-CUD

1. Positive symptoms of psychosis (> 4 [moderate]) on any item of the PANSS psychosis subscale (once abstinent) except for the hallucination item. We will exclude for a rating > 5. for this item.
2. Current cocaine/stimulant dependence. (Note: Current alcohol, synthetic cannabis, nicotine, and caffeine abuse or dependence are allowed; current cocaine/stimulant or other drug abuse is allowed provided the person can achieve the required abstinence; past dependence on cocaine/stimulants or other drugs is also allowed)
3. Pharmacological treatment for addiction (e.g., disulfiram, naltrexone, acamprosate, topiramate, varenicline, buproprion) as determined by a study physician's review.
4. Mental retardation
5. History of head injury with period of unconsciousness or focal brain injury as determined by a study physician's review.
6. Metal objects within the body that would contraindicate an MRI
7. Pregnancy or currently nursing
8. Is deemed inappropriate for the study by the PI (e.g., due to other medical conditions, medication, psychiatric concerns, or other circumstances that could cause safety concerns or impair the person's ability to participate in the study.)
9. Taking clozapine
10. Any condition that would contraindicate use of cannabis or dronabinol.
11. Patients seeking treatment to limit their cannabis use.
12. History of a seizure disorder as determined by a study physician's review

13. Is assessed as being suicidal or violent as determined by a study physician's review.

Group 4 - Control participants with SCZ

1. Positive symptoms of psychosis (> 4 [moderate]) on any item of the PANSS psychosis subscale (once abstinent) except for the hallucination item. We will exclude for a rating > 5. for this item.
2. Any history of a substance use disorder other than nicotine and caffeine.
3. Pharmacological treatment for addiction (e.g., disulfiram, naltrexone, acamprosate, topiramate, varenicline, buproprion) as determined by a study physician's review.
4. Mental retardation
5. History of head injury with period of unconsciousness or focal brain injury as determined by a study physician's review
6. Metal objects within the body that would contraindicate an MRI
7. Pregnancy or currently nursing
8. Is deemed inappropriate for the study by the PI (e.g., due to other medical conditions, medication, psychiatric concerns, or other circumstances that could cause safety concerns or impair the person's ability to participate in the study.)
9. History of a seizure disorder as determined by a study physician's review
10. Taking clozapine
11. Is assessed as being suicidal or violent as determined by a study physician's review.

Groups 5-7 - Control participants with CUD

1. Any Axis I psychiatric diagnosis other than a CUD. (NOTE: Current alcohol, synthetic cannabinoid, nicotine, and caffeine abuse or dependence are allowed. Other substance abuse is allowed provided the person can achieve the required abstinence; past dependence on cocaine/stimulants or other drugs is also allowed. Also, past (but not current) diagnoses of ADHD, depressive disorders and anxiety disorders are allowed.)
2. Taking any psychotropic medication
3. Pharmacological treatment for addiction (e.g., disulfiram, naltrexone, acamprosate, topiramate, varenicline, buproprion) as determined by a study physician's review
4. Mental retardation
5. History of head injury with period of unconsciousness or focal brain injury as determined by a study physician's review
6. Metal objects within the body that would contraindicate an MRI
7. Pregnancy or currently nursing
8. Is deemed inappropriate for the study by the PI (e.g., due to other medical conditions, medication, psychiatric concerns, or other circumstances that could cause safety concerns or impair the person's ability to participate in the study.)
9. History of a seizure disorder as determined by a study physician's review
10. Is assessed as being suicidal or violent as determined by a study physician's review.
11. Has a legal guardian.
12. Any condition that would contraindicate use of cannabis or dronabinol.

Group 8 – Healthy control participants

1. Any Axis I psychiatric diagnosis (caffeine dependence is allowed)
2. Taking any psychotropic medication
3. Pharmacological treatment for addiction (e.g., disulfiram, naltrexone, acamprosate, topiramate, varenicline, buproprion) as determined by a study physician's review
4. Mental retardation
5. History of head injury with period of unconsciousness or focal brain injury as determined by a study physician's review
6. Metal objects within the body that would contraindicate an MRI
7. Pregnancy or currently nursing
8. Is deemed inappropriate for the study by the PI (e.g., due to other medical conditions, medication, psychiatric concerns, or other circumstances that could cause safety concerns or impair the person's ability to participate in the study.)
9. History of a seizure disorder as determined by a study physician's review
10. Current tobacco smokers
10. Is assessed as being suicidal or violent as determined by a study physician's review.
11. Has a legal guardian.

Note: Since the overwhelming majority of patients with SCZ smoke cigarettes (as do many with CUD), we will allow participants in Groups 1 – 7 to be tobacco smokers and we will control for smoking in our data analysis (see below). We exclude current tobacco smoking in the normal control participants since the fact of cigarette smoking could select participants with a dysregulated BRC as a basis for their cigarette smoking.

6. *Financial Considerations:*

Disclosure of financial impact on the participant is critical to informed consent. Insurance cannot be billed for research-related services outside the standard of care or paid for by the funding agency for the study. The department, the study or the participant may be responsible for payment for research-related services. Participants should know which tests, visits, or procedures will be billed to them or their insurance and which ones will be paid by the funding agency for the study or the department.

a) *List tests, visits, and procedures performed for only research purposes. These services are outside the standard of care. They would not be performed if the individual were not a research participant, and may not be billed to a health insurance plan.*

Note: 6a information must also be in "How is this different . . ." section of the consent form.

This is not a treatment study. All tests and procedures for this study are performed only for research purposes outside of standard care and will not be billed to the participant or his/her insurance.

b) *List the tests, visits, and procedures that may be standard care, but for which the funding agency for the study is paying.*

None

c) *Will the funding agency for the study be responsible for the above costs?*
☒ *Yes* ☐ *No* *If No, describe who will be responsible (i.e., department or participant).*

7. *Statistical Methods and Review Statement:*

a) *Specify the primary endpoint, as well as other endpoint(s).*

- Activation of BRC (particularly the nucleus accumbens) in anticipation of monetary reward.
- Resting state connectivity within the BRC
- Scores on the Rewards Responsiveness task

b) *State the statistical analysis plan, including all hypothesis tests (e.g., t-test, chi-square), and estimation methods related to the primary endpoint. If a formal protocol for the study exists, page references to the protocol are acceptable.*

We will assess participants comprising 8 groups at Time 1 (T1) and Time 2 (T2): Group 1 (G1) –SCZ-CUD given placebo dronabinol and active cannabis; Group 2 (G2) –SCZ-CUD given active dronabinol and placebo cannabis; Group 3 (G3) –SCZ-CUD given placebo dronabinol and placebo cannabis; Group 4 (G4) –SCZ given no intervention; Group 5 (G5) – CUD given placebo dronabinol and active cannabis; Group 6 (G6) –CUD given active dronabinol and placebo cannabis; Group 7 (G7) –CUD given placebo dronabinol and placebo cannabis; and Group 8 (G8) –normal control participants given no intervention.

Aim 1 (Time 1 Group Differences): To determine whether at T1 dual diagnosis patients with SCZ-CUD (G1 - G3 combined) show (as compared to normal controls, G8):

(i) reduced fMRI activation of BRC (particularly the nucleus accumbens) to anticipation of monetary reward, as determined via group mixed effects ANOVA on contrasts of interest (e.g., anticipating reward > anticipating no reward);

(ii) decreased resting state connectivity within the BRC as evaluated using the Statistical Parametric Mapping Version 8 (SPM8) mixed effects ANOVA on the Fisher-transformed r value connectivity maps derived from the nucleus accumbens seed ROI; and

(iii) impaired reward responsiveness as determined using mixed effects ANOVA on response bias scores.

In addition, we will use a group mixed effects ANOVA to explore whether they will also differ from control participants with SCZ alone (G4) and control participants with CUD alone (G5, G6 and G7) on these measures.

Aim 2a and 2c (Group by Time effects on MID and BRC related to cannabis or dronabinol): Below, we describe the analyses involving dual diagnosis patients given cannabis (Group 1 -- G1); the same pattern of analyses will be carried out for the patients given dronabinol (Group 2 -- G2). Similar analyses will also be carried out for participants with CUD alone (Groups 5, 6 and 7 – G5, G6 and G7).

The two sets of intervention effects (specific to SCZ-CUD and CUD alone) will be compared. To determine whether the dual diagnosis patients given cannabis (G1) will show differential changes in fMRI activation in specific ROIs within BRC and in RSC within the BRC between T1 and T2, we will first conduct a Group (G1, G3, G4, G7, G8) by Time (T1, T2) mixed-model repeated measures ANOVA. Predicting a significant omnibus ANOVA, we will next examine planned contrasts to address specific hypotheses: To determine whether cannabis ameliorates BRC dysfunction, we will compare brain activation/connectivity in the patient group given cannabis (G1) to that of the control groups (SCZ-CUD placebo [G3]); (SCZ alone [G4]; CUD alone placebo [G7]; and normal controls [G8]) using a Group (G1, G3, G4, G7, G8) by Time (T1, T2) mixed-model ANOVA followed by pairwise comparisons. The inclusion of Group 4 in this analysis will allow us to examine whether any significant cannabis effect on BRC in Group 1 (G1) is independent of any changes due to repeated testing specific to having a diagnosis of SCZ. Lastly, although not a primary hypothesis of interest, to further explore any potential placebo effect on BRC, we will also conduct a comparison of G3, G4. G7 and G8.

Aim 2b and 2c (Group by Time effects on RR related to cannabis or dronabinol): To explore whether the patients with SCZ-CUD who received cannabis (G1) will show differential changes in RR between T1 and T2 relative to G3, G4, G7 and G8, we will proceed as above for Aim 2a to assess response bias, and analogously for participants who received dronabinol (G2). Similar analyses will be used for Groups 5, 6, 7 and 8, with results compared to those obtained for patients with SCZ-CUD.

Although not aims of the study, we will assess the relationship between THC plasma levels and changes in BRC activation/connectivity following cannabis (G1 or G5) and dronabinol (G2 or G6) using covariance modeling in SPM8; we will conduct analyses to determine whether cannabis (G1 or G5) and dronabinol (G2 or G6) have comparable effects on fMRI BRC activation/connectivity using a Group (G1 or G5, G2 or G6) by Time (T1, T2) mixed-model ANOVA; and we will use cerebral blood flow values obtained from arterial spin labeling MRI as covariates in the ROI analyses of BOLD data to control for any artifactual changes in fMRI signal related to drug-induced influences on CBF.

Aim 3 a, b (Group X Time effects of dronabinol on "high", liking, craving, mood, negative and positive symptoms, EPS and cognition in SCZ-CUD: These measures (other than cognition) will be taken in patients with SCZ-CUD (G2) prior to the fMRI scan and before dronabinol pill ingestion (Pre) and immediately after the MRI scan is completed (Post). We will conduct additional analyses to test the specific hypotheses that G2 patients will show: (a) improved

mood, reduced negative symptoms and EPS, and no significant change in psychotic symptoms from Pre to Post; and (b) a greater degree of change (from Pre to Post) in these measures than will those in G3, G4, G7, or G8. For cognitive measures, in which we will use assessments at T1 and T2, we will first conduct a Group (G2, G3, G4, G7, G8) X Time (T1, T2) mixed-model repeated measures ANOVA.

c) *Justify the sample size, using the concepts of power, type I error, and effect size if applicable. If a formal protocol for the study exists, page references to the protocol are acceptable.*

For Aim 1a (i), our pilot fMRI MID data comparing 12 healthy controls and 12 patients with SCZ-CUD yielded a Cohen's d of 1.10 during anticipation of reward for the accumbens ROI. For Aim 1a (ii), our pilot data on group differences in baseline RSC (12 SCZ-CUD; 12 controls), indicated effect sizes ranging from 0.84 to 1.28. For Aim 1a (iii), our pilot data on reward bias revealed a d of 0.77 for the group difference. Based on the above, we expect Aim 1a to be well powered (for 75 patients with SCZ-CUD and 25 normal controls) with effect sizes of $d \geq 0.7$ detectable with adequate power (≥ 80%). For Aim 1b, the fMRI/MID studies of Juckel et al. showed deficient accumbens response during the MID task in patients with SCZ (without CUD), 4, 5, 8 with d's of 1.26 to 1.60, and 10 patients and 10 controls in each study, while the MID studies of CUD alone are inconclusive.[11, 110] Moreover, there are no data available to permit estimation of effect sizes for RSC of the accumbens in patients with SCZ (without CUD) or those with CUD (without SCZ). For Aim 2a (i), our pilot data on the effects of smoked cannabis (N = 6) and dronabinol (N = 6) in SCZ-CUD on fMRI/MID indicated d's ranging from 0.78 to 2.41. For Aim 2a (ii) the effects of smoked cannabis and dronabinol in these same participants yielded effect sizes ranging from 0.83 to 1.0 for connectivity of the nucleus accumbens with other regions of the BRC. Thus, we expect that our group sample size should provide us with the ability to detect meaningful effects ($d \geq 0.7$) for both cannabis and dronabinol. Smaller effects than this are not likely to be clinically relevant. Finally, for Aim 2c we expect limited power to explore the comparative effects of cannabis and dronabinol on patients with SCZ and CUD relative to those with CUD alone.

8. *Data and Safety Monitoring:*

Describe plans for data and safety monitoring to ensure the safety of subjects and the quality of the data. As described in federal guidance "… a variety of types of monitoring may be anticipated depending on the nature, size, and complexity of the trial. In many cases, the principal investigator would be expected to perform the monitoring function." This plan should include monitoring to determine:

The progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome. Monitoring should also consider factors external to the study when interpreting the data, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study.

Note: This section does not request information related to sponsor study monitor visits. This section requires a description of an adequate data and safety monitoring plan.

The Dartmouth Department of Psychiatry has a Data Safety Monitoring Board (DSMB) to independently oversee clinical trials and other studies. The DSMB for this study will be composed of at least three people and will include (at minimum) a clinician knowledgeable about schizophrenia and substance use disorders, an investigator familiar with fMRI, and a biostatistician, all of whom will be independent of the study group. The group will follow the NIH policy for data and safety monitoring and guidelines as published on http://www.miaid.nih.gov/dmid/clinresearch/dsm.htm. Study data regarding participant enrollment, characteristics, symptoms, substance use, adverse events and serious adverse events will be submitted to the DSMB twice yearly for review and analysis. The DSMB will review study data to oversee the safety of study participants and conduct of the study. It will advise the PI (and the Departmental Research Committee) on continuation of the study and provide reports to the IRB regarding recruitment of appropriate participants and presence of adverse effects.

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9. *Genetics:*

Does any part of the study involve genetic analysis of biological specimens?

☒ *Yes* ☐ *No* *If yes, respond to* ***Genetics Attachment C***

10. *Instruments:*

Describe each instrument, if any, used to collect data in this study.

Attach copies of any questionnaires, surveys, or interview questions. If the research involves interviews that could evolve as the research progresses, include a list of discussion topics and any "starter" questions for each topic that can reasonably be expected to be covered. If a draft of a written questionnaire or survey is attached, it should be clearly labeled as such and a final version should be sent to CPHS for review before data collection begins.

Pre-screening: As part of our recruitment, a short, web-based survey will be used to prescreen people interested in participating in the study. The survey will ask a series of questions targeting the most common and clearly defined criteria for inclusion (e.g., age, willingness to be abstinent during the study, current cannabis use). The screening survey will provide feedback as to whether or not people may be eligible to participate and collect contact data on those appearing eligible. The results of the survey will be for recruitment purposes and not a part of the study data.

Diagnosis: We will do an all-source Structured Clinical Interview for DSM-IV-TR (SCID) [157] to ensure each participant meets the appropriate diagnostic criteria for his or her group. Use of the DSM-IV will allow us to have a consistent measure across both the previous pilot study and this one (and the DSM-5 SCID is not yet available). The SCID-II module for Antisocial Personality Disorder will be used to detect whether or not participants meet criteria for this disorder. Research suggests that trauma may change reward circuitry. We will therefore track trauma exposure using the PTSD Screening Questionnaire and use these data as covariates in our final analyses.

Substance Use: We will use the Timeline Follow-Back (TLFB) calendar to establish use of cannabis or other substances following the recommended method of Sobell.[173]

Psychiatric symptoms: We will use the PANSS (Positive and Negative Syndrome Scale)[174] to assess psychiatric symptoms, as well as positive and negative symptoms. The Barkley Adult ADHD Rating Scale-IV (BAARS-IV; Barkley, 2011) will be administered during the Baseline Neuropsychiatric Testing visit to assess current symptoms of attention deficit.

Neurological symptoms: Extrapyramidal system effects will be assessed with the Simpson-Angus Scale (S-A),[175] the Abnormal Involuntary Movements Scale (AIMS),[176] and the Barnes Akathisia Scale.[177]

Cannabis-related effects: We will employ a brief version of the visual analogue self-report scale (VAS) used by our consultant, Dr. Haney, in her studies of cannabis use.[14, 178, 179] The VAS will be used to rate mood, "high" and "liking". The Cannabis Withdrawal Assessment Scale will be utilized at each visit while participants are establishing abstinence from cannabis.

Cannabis craving: The 12-item self-report Marijuana Craving Questionnaire (MCQ-12) will be used to rate craving for cannabis.[180, 181] We will use the total score for our analyses.

Intellectual Functioning: Study participants will complete the Wide Range Achievement Test – 4 (WRAT–4) reading subtest[183] at screening as an estimate of premorbid intellectual functioning.

Baseline Neuropsychiatric Assessment: Intellectual assessment: Handedness will be measured using the Edinburgh Handedness Inventory (Oldfield, 1971). This 10 item questionnaire asks participants to rate the extent to which they prefer to use one hand or the other to complete a series of tasks. The Computerized Iowa Gambling Task (Bechara, 2007) task involves decision making under conditions of monetary reward and punishment. It has been often used in studies of schizophrenia and of substance use disorders. Inhibitory control will be assessed using Stop Signal Task (Logan, Cowan, & Davis, 1984), which has been extensively studied in clinical populations. The Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995) will be used as a measure of impulsiveness.

Brief Repeatable Cognitive Test Battery: Participants will complete a brief test battery to assess the effects of cannabis and dronabinol on cognitive functioning. This battery will include: the Hopkins Verbal Learning Test - Revised[184] and the Brief Visuospatial Memory Test-Revised,[185] which each have six equivalent alternate forms; the Symbol Digit Modalities Test, which has four equivalent alternate forms;[186, 187] the Delayed Discounting Questionnaire (Heerey et al.,

2007) to measure impulsivity; the WAIS-III Letter Number Sequencing (Weschler, 1997) to assess verbal working memory which has been shown to be impaired in persons with schizophrenia; and the Continuous Performance Test - Identical Pairs Version (CPT-IP) (Cornblatt, Risch, Faris Friedman & Erlenmeyer-Kimling, 1998) to assess attention and working memory.

Probabilistic Reward Task : Participants will be studied with the Probabilistic Reward Task of Pizzagalli and colleagues,[93] which has adequate test-retest reliability[93, 96] and has been used extensively to study RR in SCZ.[73, 93, 95, 98] As suggested by the literature on RR, we will add the Perceived Stress Scale.[189-191]

Assessment of THC and other substances: Dip stick analysis of urine will be performed to assess cannabis and other substances; alcohol will be assessed with a breathalyzer. To further ensure abstinence for cannabis, we will also use an assay for urinary THC to help confirm continued abstinence. Plasma THC will be assayed by Gas Chromatography/Mass Spectroscopy- Selective Ion Monitoring (GC/MS/SIM) quantitation. Nicotine levels will be assessed at each scan day to control for possible effects of nicotine and nicotine withdrawal on the brain reward circuit.

Safety Assessment - Participants in Groups 1-3 and Groups 5-7 will have a baseline medical history and physical assessment to rule out medical contraindications to administration of dronabinol or cannabis. The assessment will include blood pressure, electrocardiogram (EKG), complete blood count and blood chemistry screen. All women in the study will have a pregnancy test at screening and before the scan on each scan day. Adverse events and medications that participants are receiving outside of the course of the study will be tracked and reviewed at each visit.

Other: The Behavior Rating Inventory of Executive Functions - Adult version (BRIEF-A) will be administered to gauge subjective integrity of executive functions in everyday life over the past month (Roth, Isquith, Gioia, 2015). This 75 item questionnaire takes about 10 minutes to complete. Participants will complete the measure once at the T1 session.

11. Deception.

Will deception of participants, including withheld information, be used in this research?

☒ *Yes* ☐ *No*

If yes, complete a-d.

a) *Describe the deception being used in this study:*

The nature of the monetary incentive delay task and probabilistic reward task requires subjects to respond believing the speed of their response is linked to the money they earn. However all participants will receive $35.00 for completing each of the two fMRI monetary incentive delay tasks and a total of up to $50 for completing the three

probabilistic reward tasks, regardless of their task performance (which is based on accuracy and speed) . The instructions participants are given for the task, however, do not indicate this, but rather only say that they can win money based on their performance.

b) *Explain why deception is necessary in this research:*

We decided to fix the amount of winnings on each task, and thus deceive participants, so as to not disadvantage the participants with schizophrenia who tend to respond more slowly and with less accuracy than normal controls because of their illness (or related issues such as medications). Participants will not be aware that everyone receives the same amounts because it is essential in the study of reward circuitry that they believe they are "winning" additional funds, and that their winnings are dependent upon performance. This technique is used routinely by researchers across the world in order to study brain reward circuitry. Use of the same technique allows researchers to compare results across studies.

c) *Describe the information provided to subjects when they decide to participate:*

As stated above, the instructions participants are given for the task say that they can win money based on their performance.

d) *Describe how the subjects will be provided with additional pertinent information after participation (debriefing):*

We will simply let participants know how much money they "won". We cannot debrief participants and tell them that the earnings were fixed because we believe that participants may tell other participants and that this knowledge would then interfere with the consistent measurement of brain reward circuitry between patients.

12. *Enrollment:*

a) *Estimated number of participants for duration of entire study:*

At Dartmouth or associated sites: Female: 100 *Male:* 300

If Multi-center study: Estimated total number at all sites: 400

b) *Estimated age range of participants:* 18-55

13. *Timetables:*

a) *Indicate length of participant involvement in the study:* Approximately 4-6 weeks

b) *Estimate how long it will take to enroll enough participants to complete this study:* 5 years

14. *Risks:*

The purpose of this section is to determine if subjects will be placed "at risk," which in general means

exposed to the possibility of physical, psychological, social, economic, legal, dignitary or other harm as a consequence of any activity proposed in the research project.

a) What is the overall risk classification of the research?

- ☐ *Minimal*
- ☒ *Greater than minimal*
- ☐ *Significant*
- ☐ *Unknown*

Note: In the federal regulations on human subjects protection minimal risk means "The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

b) *Describe any potential risks (physical, psychological, social, legal, economic, or other) and assess their likelihood and seriousness. Describe the procedures for protecting against or minimizing these risks, including risks to confidentiality, and assess their likely effectiveness. Please list risks from most severe/likely to least severe/unlikely.*

Overall Approach to Protecting Study Participants: The PI and the DSMB will monitor safety throughout the study. We will obtain careful informed consent and insure that each participant fully understands the study procedures and the fact that for participants with SCZ-CUD both cannabis and dronabinol may cause a transient increase in symptoms and side effects. Confidentiality will be maintained with the standard procedures described below. A participant's clinical status will be monitored throughout the protocol and care will be coordinated with each person's clinical treatment team. Study participants may discontinue a study procedure at any time if they are uncomfortable or the study procedures appear to be causing exacerbation of illness.

Risk of potential exposure to COVID-19

Due to the pandemic beginning in 2020, there is a risk of potential exposure to COVID-19. For participant safety and safety of study staff we will follow all Dartmouth-Hitchcock procedures to reduce risk of infectious disease transmission. As of April 2021, we will use the following procedures during all study visits, and procedures will be adjusted as recommended by Dartmouth-Hitchcock.

- DH employees (potential participants and study staff) will complete any COVID-19 risk screening requirements per DHMC policy (currently on-line screening or in-person with door screeners) prior to entering the building.
- Non-DH employees will be screened at entrances staffed with door screeners.
- Whether they participate in on-line or in-person screening, the participant and all study staff must meet all DH COVID-19 screening requirements in order to be allowed into the medical center. If the participant/staff has symptoms or risk of exposure, research visits will not take place until the situation has resolved.

- Participants and all study staff will be required to wear a facial mask over their nose and mouth. If the participant does not have one, they will be provided with one. Participants will be required to wear the mask at all times with the exception of while they are in the MRI scanner. Study staff will also wear eye protection.
- Surfaces and equipment will be cleaned per medical center policy
- Study staff will practice frequent handwashing per DHMC guidelines.
- Social distancing of a minimum of 6 feet will be maintained with the exception of procedures requiring closer contact such as obtaining vital signs, placing the IV and obtaining blood specimens, getting the participant positioned in the MRI scanner and during some of the neuropsychological testing.
- If for any reason we feel it is unsafe for the participant or study staff to continue with the study visit we will cancel the visit and work to reschedule as soon as we feel it is safe to conduct the visit.

Risks from Cannabis and Dronabinol - Symptom Exacerbation: In this study, the most prominent activity associated with risk is the administration of cannabis and dronabinol, particularly to Groups 1, 2 and 3 who have a diagnosis of SCZ and a co-occurring CUD. Multiple strategies will be used to protect patients with SCZ-CUD who are given cannabis or dronabinol (or double-blinded cannabis and placebo) from relapse of psychosis. First, patients will be under treatment for their psychosis during the study, and must be stable with a low level of symptoms in order to participate. Second, all participants who will be exposed to cannabis or dronabinol during the study will be current active cannabis users who are used to the effect of cannabis. Third, with our pilot work, we have established a safe dose of dronabinol (two 7.5 mg capsules) and of cannabis for the cigarette for these patients, which did not produce untoward effects. We will use these doses in this study. All participants given cannabis or dronabinol (or double-blinded placebo cannabis and dronabinol) will be monitored closely in the laboratory until it is determined by the MD that they are able to be safely discharged. If symptoms develop and do not remit, patients will be offered inpatient treatment, as appropriate. Moreover, for participants given cannabis, dronabinol or placebo, we will attempt to contact them both the day after T2 and one week later to assess their status. If additional check-ins or clinical interventions are needed, it will be coordinated by the study team. In our pilot study with 15 patients in a similar protocol, none had problematic symptoms and no patients required additional medication or inpatient treatment. With the use of the strategies described here, study participation is unlikely to precipitate significant symptom exacerbations, but research staff, who have substantial clinical experience with this population, will be prepared to act immediately to treat patients and maintain safety if an exacerbation does occur.

Risks from Cannabis and Dronabinol - Other: Known effects of dronabinol and cannabis are listed below. These side effects occurred when people took dronabinol regularly. They are also known to occur when people smoke cannabis. We do not know how likely it is that these

side effects will occur if the medication is taken once as it will be in this study. Participants will be monitored frequently in the lab all day on the days they take these drugs.

Common side effects: A "high" feeling (e.g. laughing easily, feeling happy, having a heightened awareness)

Occasional side effects (reported in 3-30% of people: Paranoia, confusion, nervousness, sleepiness, dizziness, stomach pain, nausea with or without vomiting, tachycardia, flushed face

Rare side effects (reported in less than 3% of people): Red eyes, diarrhea and/or incontinence, depression, nightmares, trouble speaking, visual problems, ringing ears, low blood pressure

Seizures have been reported in people taking dronabinol. Patients with a history of a seizure disorder will be excluded from this study.

Recruited patients with dual diagnosis and participants with CUD (without schizophrenia) will all be frequent cannabis users. Thus, we do not expect anything more than minimal effects from the modest dose of THC in the cannabis cigarettes or the two 7.5 mg dronabinol capsules. However, as with the potential of symptom exacerbation in the dual diagnosis patients (above), we will monitor all CUD patients until it is determined by an MD that they can be safely discharged and be prepared to act immediately to provide treatment and to maintain participant safety. Moreover, participants in Groups 1-3 and Groups 5-7 will have a baseline medical history and physical assessment to rule out medical contraindications to administration of dronabinol or cannabis. The assessment will include blood pressure, EKG, complete blood count and blood chemistry screen. All women in the study will have a pregnancy test as described in the section on assessments.

Risk Related to Confidentiality: This research involves monitoring and treatment of patients who use cannabis, an illegal substance. Participants may engage in other illegal activities. Maintaining confidentiality is an area of utmost importance for this population.

To minimize risk of divulging confidential information regarding substance use or other illegal activities as well as other study information, strict attention to confidentiality will be maintained throughout every aspect of this research with standard policies and procedures, and a Certificate of Confidentiality (provided by NIDA). All members of the research team will follow the procedures to protect confidentiality adhered to by research groups at Dartmouth per the Dartmouth Committee for the Protection of Human Subjects (CPHS). Interested participants will provide permission in the form of release of information for study personnel to contact treating clinicians to discuss appropriateness of the participant's participation in the study. Participant data will be coded to protect privacy. Each patient will be assigned a unique identification number. The list of participant names and identification

numbers will be kept in a locked file cabinet separate from the database. Access to the computerized data system is carefully protected by a secured password entry system. Participants will be made aware of the various parties who will have access to their data in the informed consent document. Access to participants' data will be restricted to project investigators and other study staff on a need to know basis. Patient information, if reported, will be reported as group data or anonymously in case reports. No patients will be individually identified.

Risks from Research Assessments: The assessments being used in this study (i.e. measures of substance use, symptoms, measures of "high", mood, "liking", reward responsiveness, cognition, urine and blood assessments) may cause some discomfort, boredom, anxiety or fatigue. It is also possible, but not likely, that the SCZ participants may experience an increase in their underlying symptoms due to the process of research assessments.

Participants will be advised that they can take a break, refuse to answer question(s), or end the study session if they become uncomfortable in any way. Research staff will involve a referral site clinician to provide consultation if a patient becomes more symptomatic during a study procedure. All participating mental health agencies have emergency services that can be accessed at any time if the participant's regular clinicians are unavailable. Additionally, psychiatrists experienced in the treatment of this population, will be present or rapidly available via pager for emergency consultation at any time.

Risks from Blood Draws:
Drawing blood may involve some discomfort; the needle-stick can be slightly painful, and can cause bruising, a feeling of faintness, and in rare instances, infection at the site of the blood draw. Proper technique will be used by trained staff to minimize the likelihood of these problems. A low dose of lidocaine delivered to the skin or subcutaneously will be offered to reduce the discomfort of placing the intravenous cannula. When used in this fashion, the risks of lidocaine include:

Common: Flushing, redness of skin, swelling of skin, warm skin

Less common: Bruising, pain, itching, nausea, vomiting

Serious allergic reactions can occur. This medication should not be used for persons with a history of allergy to lidocaine or related medications.

Risks from the fMRI procedure: The scanner produces a loud banging noise and may be uncomfortable for people who have claustrophobic-like reactions in confined spaces. The long-term risks of 2 MRI scans of the brain are unknown.

Participants will be screened for metallic implants or any magnetic devices on or in their bodies prior to inclusion in the study to help ensure safety when in the MRI scanner. Participants will be warned about the possible discomforts related to MRI scanning and will be advised regarding strategies for managing these discomforts. Participants may view the scanner and scanner room prior to participation to habituate to the environment. Rest breaks will be provided as needed. Guided relaxation exercises will be provided as needed should anxiety be elevated. Participants can terminate their participation should a strong reaction occur.

Risks from Cannabis Withdrawal: Heavy cannabis users who discontinue use during the study may experience symptoms of cannabis withdrawal, involving nervousness, sleep disturbance, and appetite changes. Withdrawal from cannabis is not medically dangerous, and does not result in known long-term negative consequences. Since patients with schizophrenia tend to be light users of cannabis, we do not expect substantial cannabis withdrawal symptoms in our dual diagnosis participants. Some CUD (without SCZ) participants, if they are heavier users, may experience some withdrawal symptoms.

Participants will be educated about cannabis withdrawal with a fact sheet that includes a brief list of coping strategies. If participants experience cannabis withdrawal, research staff will cue the participant to use coping strategies and, if needed, will link the patient with clinical support from their treatment team (for patients with SCZ-CUD) or from clinical staff at DHMC (for participants with CUD alone).

Risks to Fetuses and Nursing Infants: Cannabis is known to be harmful to fetuses. Dronabinol is a pregnancy category C medication. The risks of brain fMRI for pregnant or nursing mothers to fetuses and to nursing babies are unknown. Thus, pregnant or nursing mothers will not be included in the study.

A urine pregnancy test, paid for by the study will be given to all women at the initial assessment, and on the morning of each scan day (i.e., thus before administration of cannabis, dronabinol or placebo and before scanning). If a participant is pregnant at baseline or becomes pregnant, she will be informed immediately, referred to her psychiatrist and/or her primary care physician, and discharged from the study. She will not undergo scanning nor be given cannabis or dronabinol.

Risks Related to Genetic Testing: The risks from genetic testing are mostly related to confidentiality and others (e.g. an insurer) learning a participant's results. To protect them from this type of risk, test results will be kept private. Information about participants will be coded with a number, not their name. Only the researchers in this study will be able to know the results of testing. The results of the genetic test will not be told to participants, treatment providers or other's outside of the study. The results of the test will not be included in participants' medical records.

Risks Related to the Eye Camera: The eye camera LED light emits in the infrared range of the spectrum. Because the eyes do not register infrared light, it is important when using any infrared source to ensure that exposure levels on the retina, lens, or cornea will not be large enough to cause damage (e.g., burns). The LED used in the device has a much lower radiation emission than the limits defined in the appropriate standards (U.S. ANSI IESNA 27 and international IEC 62471, which govern non-laser lamps and lamp systems and their effects on eyes and skin). Specifically, at the deployment distance of 50mm or more from the eye, the intensity will be less than 4W/sr, and thus these LEDs belong to the "exempt group," considered to be of "no photobiological hazard". At a distance of 35mm or closer, the intensity would qualify as "low risk", but we will maintain the camera at a minimum of 50 mm using a fixed deployment on the head coil to ensure safety.

15. *Risk/Benefit analysis:*

Describe why the risks to subjects are reasonable in relation to the anticipated benefits to participants and in relation to the importance of the knowledge that may reasonably be expected to result from the study.

Participation in this study is associated with a variety of possible risks, but none of them are severe. We will obtain careful informed consent to insure that every potential participant fully understands all of the possible risks. In addition, we will not include individuals who we believe would not be able to tolerate the study procedures.

Those groups that will receive dronabinol or smoke cannabis already have a diagnosis of a CUD with recent use. For Groups 1, 2 and 3, who have comorbid diagnoses of SCZ, the use of these substances is unlikely to precipitate symptoms or side effects that are new or unusual to the participant. That was demonstrated quite clearly in the pilot study we completed. For those persons with a CUD but not SCZ, we do not believe the use of this strength of cannabis or dose of dronabinol will be unusual for them or cause any untoward effects. In the event that this is not the case, we have established intensive monitoring procedures that will allow us to detect instances in which a participant experiences adverse effects. Overall, using these strategies, we believe the risks related to participation in this study are low.

Data collected from this study will begin to improve knowledge regarding the biologic basis of cannabis use in patients with schizophrenia. Since schizophrenia is a severe disorder, and the co-occurrence of cannabis use disorder in this population presents as a significant public health problem. Cannabis use disorder contributes to the morbidity of schizophrenia through increased relapse and hospitalizations, noncompliance with treatment, and poorer overall functioning. The literature suggests that cannabis use in patients with schizophrenia may be related to cannabis' activation of brain reward circuitry, which may be dysfunctional in patients with schizophrenia. No medication treatments are currently available for the treatment of cannabis disorders, and the one medication that appears to decrease cannabis use

in patients with schizophrenia, clozapine, has side effects with severely restrict its use. The data gathered in this study will begin to expand knowledge regarding the biologic basis of cannabis use in schizophrenia, as well as to test whether dronabinol may correct the reward circuitry deficits thought to underlie this frequent, serious comorbidity. If data from this project suggest that dronabinol does improve reward circuitry impairments, it could become a candidate for study as a possible treatment for cannabis disorders in patients with schizophrenia.

The overall risk from study participation is generally low as described above. We believe that a rigorous informed consent process, in combination with the procedures described above, are adequate to prevent potential risks and to mitigate potential negative impacts of the research.

16. ***Research Setting***

a) *Is this a multi-center study?*

☒ *Yes* ☐ *No*

If yes: Are you the lead investigator? ☐ *Yes* ☐ *No*

If you are NOT the lead investigator:

Name of lead investigator:

Institution where the lead investigator is located:

b) *List all sites where research will take place and the CPHS at Dartmouth College is the reviewing IRB (e.g. DHMC Alliance Hospitals, DHMC Clinics, WRJ VAMC):*

Participants with SCZ for the study will be recruited from DHMC and affiliated hospitals, community mental health centers, and DH affiliated clinics. Recruitment sites participate in a clinical research network organized by the Dartmouth Psychopharmacology Research Group, of which Dr. Brunette is the Director. These sites include DHMC, Dartmouth Affiliated Clinics, Mental Health Center of Greater Manchester, West Central Behavioral Health, Monadnock Family Services, Merry Meadows Farm, Clara Martin Center, Healthy Perspectives - Innovative Mental Health Services, Riverbend Community Mental Health Center, Greater Nashua Mental Health Center, Health Care and Rehabilitation Services of Southeastern Vermont, Substance Abuse Treatment Center/ University of Vermont and Rutland Regional Medical Center. All MRI scans and all cannabis, dronabinol, and placebo administrations will take place at DHMC and UVM .

c) If you are the lead investigator of a multi-center study, *list all sites where research will take place and the CPHS at Dartmouth College is* ***NOT*** *the reviewing IRB:* *or check* ☐ *N/A*

Note: Each site taking part in the research should have appropriate institutional or IRB oversight. A Site Agreement or Federalwide Assurance may be required. The CPHS office can assist you with these arrangements.

University of Vermont Medical Center under Dr. Michael Scott Mackey, as site PI.
White River Junction Veterans Administration Medical Center under Dr.James Rustad, as site PI.

d) *Does the study involve sites outside of the United States and Canada?*
☐ *Yes* ☒ *No*
If yes, are arrangements for the international site(s) being made by a multinational pharmaceutical or device sponsor or a cooperative oncology working group?
☐ *Yes* ☐ *No*
If no, please ***complete Attachment L****.*

17. ***Adequacy of Resources to Protect Subjects:***
a) Investigator (including co-investigators) has sufficient time to conduct and complete the research.
☒ *Yes* ☐ *No*

b) Adequately qualified (including experience, training, supervision, and familiarity with the protocol) staff are available for this research.
☒ *Yes* ☐ *No.*

c) Describe availability of psychological, social, or medical services, which include counseling or social support services, that may be required as a consequence of research participation.

Study participants who have schizophrenia disorders will be engaged in treatment for their schizophrenia illness and will have access to their psychiatric prescriber and community mental health treatment team. Additionally, Drs. Mary Brunette, or other psychiatrists, will be available should adverse events occur that require assessment and intervention.

d) *Describe psychological, social, or medical monitoring, ancillary care, equipment needed to protect participants (e.g. close proximity to resuscitation equipment or a plan for monitoring of emotional state during study procedures).*

Intensive monitoring will occur throughout each Study Day as described in the protocol.

e) *Describe other resources needed for the protection of subjects in the conduct of this research (e.g. language translation services).*

None

f) *Explain how the investigator has access to a population that would allow recruitment of the required*

number of subjects.

Participants with schizophrenia or schizoaffective disorder (SCZ) will be recruited from the Dartmouth affiliated sites listed above, which treat more than 3000 such patients. Estimating that 33% of these participants have CUD, we expect to have a base of > 1000 participants from which to recruit. The most recent NH state data suggest that 7% of patients with SCZ are taking clozapine; thus, we expect that approximately 930 patients with CUD will be eligible for this study. We expect to exclude about 20% of the eligible sample because of previous head injury or other contraindications, leaving approximately 720 patients. Since our experience indicates that at least 50% of those eligible are willing to enter imaging studies that include a period of abstinence, we expect to have a sufficient number of participants to recruit a sufficient number of participants so that we can complete the study on 75 dual diagnosis participants (Groups 1, 2, and 3). There will also be sufficient patients for Group 4 (SCZ without CUD). Recruitment of those with CUD without SCZ *(Groups 5, 6 and 7)* and normal control participants *(Group 8)* will occur through advertising and the use of flyers.

18. *Participant Population:*

Certain populations are considered vulnerable to coercion and undue influence. These populations are provided with additional protections when participating in a research study. The populations include:

- *prisoners*
- *human embryos*
- *fetuses*
- *elderly people*
- *people with an cognitive disability (also see #24 below)*
- *people with a disabling psychiatric illness*
- *people who are economically disadvantaged persons*
- *people who are illiterate*

Refer to: *Students, Employees* ***Attachment D***
Illiterate Subjects ***Attachment E***

a) *List vulnerable groups:* *or check* ☐ *None*

We are studying people with schizophrenia, who are typically disabled by their psychiatric illness and are often economically disadvantaged. We do not anticipate recruiting Illiterate participants, but cannot rule it out. If this occurs, we will follow the CPHS guidance (see Attachment E). Some persons who are employees of Dartmouth, DHMC or our recruitment sites may wish to participate in this study.

b) *Describe additional protections:* *or check* ☐ *N/A*

We will utilize all of the strategies we typically use in our studies of individuals with serious mental illness. We will conduct a careful informed consent. People who are unable to provide informed consent due to a lack of clear understanding of the potential risks (or for other

reasons) will not be included in the study. We have a system of careful monitoring and backup treatments and supports to employ should a participant have difficulty, including a 24 hour availability of clinicians and psychiatrists who are experienced in the treatment of persons with co-occurring schizophrenia and cannabis use disorder. Because many participants do not have regular telephone service, thereby limiting their access to our emergency number, we will provide those participants who express the need for a telephone with a prepaid cellular phone (e.g. Tracfone) for use during the study. This telephone would also be used for reminder calls and in case the doctor and participant agree that a telephone check-in is warranted. To avoid exploiting persons who are economically disadvantaged, we are not making the stipend provided to participants unduly high. It is similar to what was offered in our previous study. In terms of students and employees who wish to participate in this study, we are not specifically recruiting these populations but also would not deny them access to the study. They would have the same careful protections to the confidentiality of their data as other participants and the consent forms clearly spell out the issues of who has access to study data.

19. *Gender and Racial/Ethnic distribution:*

NIH guidelines state that research involving human participation should include minorities and both genders.

Note: If one gender or minorities are excluded or are inadequately represented in this research, particularly in proposed population-based studies, a clear and compelling rationale for exclusion or inadequate representation should be provided.

Will eligibility for the study be based on gender, race, or ethnicity? ☐ *Yes* ☒ *No*

If yes, explain:

20. *Pregnant Women:*

Are pregnant women eligible for enrollment into this study? ☐ *Yes* ☒ *No*

If yes, respond to ***Research Involving Pregnant Women, Fetuses and Neonates: Attachment M***

If no, explain and include a process to determine pregnancy status. If a pregnancy test is required, note who will pay:

As described elsewhere in this document, pregnancy tests paid for by the study will be conducted on all female participants.

21. *Fetuses and Neonates:*

Are fetuses and neonates participants in the research?

☐ *Yes* ☒ *No*

If yes, respond to ***Research Involving Pregnant Women, Fetuses and Neonates: Attachment M***

22. Children:

Are children eligible for enrollment into this study? Under state law, a child is a person less than 18 years old.

☐ *Yes* ☒ *No*

If yes, respond to ***Children: Attachment F***

If no, present an acceptable justification for the exclusion:

Note: NIH guidelines state that research involving human participation should include children unless there is appropriate justification for their exclusion. The investigator should address the rationale for selecting or excluding a specific age range of children, or an explanation of the reasons for excluding children as participants in the research. When children are included, the plan should also include a description of the expertise of the investigative team for dealing with children at the ages included, of the available facilities to accommodate the children, and a sufficient number of children to contribute meaningfully to the study analysis.

We have elected to exclude children (those under the age of 18) because schizophrenia in younger children is rare and the treatment of childhood-onset schizophrenia requires specialized management involving comprehensive social and family support services. Moreover, there may be increased risks of giving cannabis to young adolescent children (below the age of 18).

23. *Women of Child-Bearing Capability*

Are women of child-bearing capability eligible for enrollment into this study?

☒ *Yes* ☐ *No*

If yes, describe potential harm to an unborn fetus from study activities and the process for determining pregnancy status if necessary. If a pregnancy test is required, note who will pay. If there is potential harm to an unborn fetus, the investigator should review with each individual a plan to avoid pregnancy. If the investigator regards these contraceptive plans as inadequate, the individual should be advised on how to achieve adequate contraception or should be excluded from the study.

Cannabis is known to be harmful to fetuses. Dronabinol is a pregnancy category C medication. The risks of brain fMRI for pregnant or nursing mothers to fetuses and to nursing babies are unknown. Thus, pregnant or nursing mothers will not be included in the study.

A urine pregnancy test, paid for by the study will be given to all women at the initial assessment, and on the morning of each scan day (i.e., thus before administration of cannabis, dronabinol or placebo and before scanning). If a participant is pregnant at baseline or becomes pregnant, she will be informed immediately, referred to her psychiatrist and/or her primary care physician, and discharged from the study. She will not undergo scanning nor be given cannabis or dronabinol.

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24. *Individuals With Impaired Decision-Making Capacity:*

a) Will participants potentially lacking capacity to provide informed consent be eligible to enroll in this study? ☒ *Yes* ☐ *No*

b) Is it likely study participants may lose their capacity to provide informed consent during the conduct of the study? ☐ *Yes* ☒ *No*

If yes to a or b, respond to ***Research Involving Individuals with Impaired Decision-Making Capacity: Attachment G***

25. *Recruitment:*

Describe how subjects will be recruited for participation in this study:

Eligible participants may be identified from medical record information as a "preparatory to research" activity under the HIPAA Privacy Rule. Protected health information obtained as a preparatory to research activity may not be removed by a researcher from DHMC, including on mobile electronic storage devices. Contact with the identified participants, however, may not occur without prior CPHS approval of the recruitment plan for the study. This plan should describe how initial contact with participants will be made and by whom. Please note in general, individuals should not be contacted for recruitment into a research study by someone unknown to the individual.

a) Will subjects be recruited by searching records (e.g., school records, medical records)?
☒ *Yes* ☐ *No*
If yes, will this search include paper files?
☒ *Yes* ☐ *No*
If yes, where will these paper files be located? At the various recruitment locations

If yes, will this search include electronic files?
☒ *Yes* ☐ *No*
If yes, who maintains these electronic files? The individual recruitment locations have their own electronic medical records

Dartmouth-Hitchcock Recruitment Procedure

Under the "preparatory to research" activity provision in the HIPAA Privacy Rule, a study team member will screen medical records using key diagnostic codes to search for potentially eligible participants age 18 to 55 with a schizophrenia or schizoaffective disorder. The team member will review the medical records to ascertain basic inclusion and exclusion criteria. If a potential subject is identified, the team member will consult with the subject's treatment provider to determine if they think the subject is stable and might be a good candidate for study participation. If deemed appropriate the provider would discuss the study with the potential subject to determine their interest. If interested the provider would get their permission to be contacted by the study team

and/or give them an approved handout describing the study with the study team's contact information.

b) Will databases be utilized?
☐ *Yes* ☒ *No*
If yes, please specify types and locations of databases:

c) Will fliers or brochures be posted, mailed or otherwise distributed?
☒ *Yes* ☐ *No*

d) Will letters be sent to potential participants?
☐ *Yes* ☒ *No*
If yes, please provide the letter(s) for CPHS review.

e) Will referral be utilized for recruitment?
☒ *Yes* ☐ *No*
If yes, please be aware patients should first be informed about the study and agree to the contact before any referral.

f) Will any other method be employed?
☒ *Yes* ☐ *No*
If yes, please specify, in detail, what those methods will be:

Normal control and CUD without schizophrenia participants (Groups 5-8) will be recruited not only through flyers, but also through advertisements on the radio, in newspapers, and on the internet.. Some internet based advertising will use sites such as Facebook and Google ads. Viewer can click on the ad and will be directed to a brief description of the study and an online survey to determine if the person may qualify for the study. (See section 10 for a description of the survey). The description will also provide viewers with a telephone number that they can call if they want to find out more about the study or whether they might qualify without completing the survey online.

Dual diagnosis participants and participants with schizophrenia without a CUD (Groups 1-4)will be recruited using the same methods as above but will also be recruited from local community mental health centers and other treatment providers. Treatment providers will be given the eligibility criteria for the study. They will be asked to contact those persons they treat who may be eligible and ask permission for the research team to contact the person. Most potential participants are open to this but it can take a month or more for this to occur. The reason for the delay is that some individuals in mental health care are only seen every two to four weeks and treatment providers can forget to ask about research. To avoid the delay, we will use a form letter from the provider to the individual stating that it is believed that the person qualifies for a study and that the

provider would like to have the researcher contact them. The participant has the option to call the provider and decline to be contacted by the researcher. Because participants with schizophrenia often do not show up for scheduled visits/ information sessions to learn about the study prior to consent, those individuals in the groups with schizoprenia (with or without a CUD) who attend their scheduled appointment to learn about the study will receive a $25 gift card, regardless of whether or not they consent to participate in the study.

g) Does the research plan include "finder fees" or incentives (bonus payment, gift certificates) offered to study personnel for enrollment of participants?

☐ *Yes* ☒ *No*

Note: As a rule, finder fees or incentives are not acceptable. Please justify any offered incentives. If incentives become available during the course of the study, please notify the CPHS.

Attach copies of any proposed flyers, posters, pamphlets, print advertisements, and scripts for on-air advertisements or telephone calls. All recruitment materials should be approved by CPHS prior to use.

Note: Advertising should not use terms such as "new treatment," "new medication," or "new drug" without explaining that the test article is investigational. A phrase such as "receive new treatments" implies that research participants will be receiving newly marketed products of proven worth. Advertisements should not promise "free medical treatment," when the intent is only to say participants will not be charged for taking part in the investigation. The CPHS will determine if the promise of treatment without charge is an inappropriate inducement for study participation. Advertisements may state that participants will be paid, but should not emphasize the payment or the amount to be paid. The advertisement should include: the name and address of clinical investigator and research facility; the condition under study or the purpose of the research; in summary form, the criteria that will be used to determine eligibility for the study; a brief list of participation benefits, if any (e.g., a no-cost health examination); the time or other commitment required of the participants; and the location of the research activities; and the person or office from whom to obtain further information.

26. *Consent Process:*

The Principal Investigator (PI) is responsible for ensuring all participants have provided informed consent to participate in this study unless the consent process is waived or altered by the CPHS. The PI may authorize other appropriately trained individuals to obtain consent from participants.

Please file the consent form in the medical record of each research participant if study participation may affect other medical treatment.

Explain how informed consent to research participation will be obtained. Please describe the consent process, including information about:

- *Who has been authorized by the PI to obtain consent*
- *The time interval between providing information potential participants about a study and having the consent form signed*
- *Any precautions taken to minimize the possibility of coercion or undue influence*

- *Plans for responding to a potential participant or a legally authorized representative who does not speak English, such as the use of a translator or a translated consent form*
- *Any aids used to simplify scientific or technical information, like a diagram*
- *Plans to accommodate the probable literacy level of potential participants*

Our group has a procedure for the consent of participants into medication studies. It allows for only physicians and ARNPs to consent participants to be in studies. Other staff may present a consent form to participants and review it with them, but a physician or ARNP must meet with the person (face-to-face or via telephone) to answer questions, and assess understanding and voluntariness prior to the participant signing the consent form. The physician or ARNP will also assess the competency to consent of each potential participant. If an individual's capacity to consent is in doubt and the person does not have a guardian, the consent process will stop. The physician or ARNP will consult with the individual's primary psychiatrist. If in the opinion of the psychiatrist, the person cannot consent and the person lacks a guardian, the person will not be recruited. If the treating psychiatrist believes that the diminished capacity is more of a transitory state, then the consent process will be tried again on another day. Potential participants are encouraged to read the consent form and ask questions. They are further encouraged to solicit input from significant others and/or care providers, if appropriate. To minimize coercion, the consent form has language that clearly spells out that participation in the study is voluntary and refusal to participate will not affect a person's health/mental health care.

Because we do not have foreign language version of all of the assessments, we do not anticipate consenting persons who do not speak English. If literacy is a problem, our group follows the Dartmouth Committee for the Protection of Human Subjects procedure for consenting persons who cannot read or cannot read well (see Attachment E.) Finally, our group makes a concerted effort to make the language in consent forms understandable to participants.

☐ *I intend to obtain consent for research participation but I am requesting a waiver for the use of a signed and dated consent form. Please respond to the criteria listed in* ***Attachment I*** *and include an information sheet based on the CPHS template.*

☐ *I am requesting an alteration of the consent process to exclude certain information that is ordinarily required. A list of the essential elements of consent to research participation is available on the CPHS website: http://www.dartmouth.edu/~cphs/tosubmit/ConsentElements.html.*
Please respond to ***Attachment H.***

☐ *I am requesting a waiver of the entire consent process and use of a consent form. Please respond to* ***Attachment H.***

Explain why any alteration or waiver to the consent process or form is necessary.

b) Authorization: *Explain how an authorization for research use of protected health information (PHI) will be obtained. PHI is individually identifiable health information obtained from a health care provider or insurance plan. In general, the HIPAA Privacy Rule permits the use or disclosure of PHI for research purposes only with an authorization from each participant whose PHI will be involved. Only when certain criteria are satisfied can the CPHS grant a waiver of authorization or of the use of a signed and dated authorization form. A waiver of authorization is necessary for recruitment procedures when patient information is used to identify and contact potentially eligible research participants. A single form may combine the essential information for both consent and an authorization. The CPHS consent template contains this combination and is available on the CPHS website at* www.dartmouth.edu/~cphs.

Check all that apply:

☐ *This study does not involve PHI.*

☒ *A single form combining an authorization with the consent form and based on the CPHS template is included with this application.*

☐ *A separate authorization form is included with this application.*

☐ *I am requesting a waiver of authorization for only the recruitment procedure. Please respond to* ***Attachment H.***

☐ *I am requesting a waiver of signed and dated authorization. Please respond to* ***Attachment I.***

☐ *I am requesting a waiver of authorization for the use or disclosure of PHI in this entire study. Please respond to* ***Attachment H.***

In your explanation of the consent process above, please include information about obtaining authorization for the research use of PHI.

27. *Privacy and Confidentiality*:

Describe the plans to protect the privacy of subjects and maintain the confidentiality of the data.

Note: Under certain circumstances, an invasion of privacy or breach of confidentiality may present a risk of serious harm to subjects (e.g., as when the research obtains information about subjects that would, if disclosed by the researcher, jeopardize jobs or lead to prosecution for criminal behavior). Under other circumstances, an invasion of privacy or breach of confidentiality can be a moral wrong

a) *Will any study activities involve an interaction or reveal information for which protection of participant privacy is necessary?*

☒ *Yes* ☐ *No*

If yes, please identify the activities and describe the plan to protect the privacy of participants. For example, a plan for protection of privacy might consist of conducting the assent process for an adolescent minor in a private setting, rather than in the presence of the minor's parent.

Participants will be asked to provide a detailed account of their use of alcohol and drugs for the period that they are in the study. Also people will be asked about past alcohol and drug use and its impact on their lives. Participants will be tested for alcohol, marijuana and other

drugs of abuse. Persons will be asked about their history of mental health symptoms. Our plan to protect the privacy of participants is described below in section C.

b) *Will the data collected in the course of the study be considered sensitive, e.g., include information about a mental health disorder, HIV status, or SS#?*

☒ *Yes* ☐ *No*

If yes, provide the rationale for why these data are needed:

The aims of the study include the collection of data about substance use and psychiatric symptoms.

If yes, could any of these data, if disclosed, damage financial standing, employability, insurability, or reputation?

☒ *Yes* ☐ *No*

If yes, will a Certificate of Confidentiality be obtained?

☒ *Yes* ☐ *No*

Any person engaged in research collecting information about illegal conduct from human research subjects may apply for a Certificate of Confidentiality. NIH provides detailed instructions for investigators wishing to make an application at http://grants.nih.gov/grants/policy/coc/index.htm.

c) *Describe specific physical, administrative, and technical safeguards employed to secure data, e.g., limitation of access to data, use of locked file cabinets, protection of computer-based data systems.*

Information gathered through interviews will be coded to a study number. The name-number code will be kept by the PI and interviewers in a locked file cabinet. Coded interviews will be kept in separate locked cabinets in research offices at the offices of the Psychopharmacology Research Group (PRG) and the scanning laboratories at DHMC and UVM.

Data will be managed according to usual procedures of the PRG and neuropsychology research groups and UVM. These procedures include careful editing and coding of interviews and other research forms prior to data entry; locked storage of original data forms at the PRG; storage of scanning data on password protected computers, software controls on all data access; and regular backup of data files. Neuropsychological testing data and imaging data sent to DHMC from UVM will be encrypted and sent securely

We have obtained a certificate of confidentiality. Additionally, the Geisel School of Medicine at Dartmouth's Department of Psychiatry is a HIPAA covered entity, so we follow those federal privacy regulations in addition to our current confidentiality safeguards.

All imaging study data are labeled with a unique study ID and the date of acquisition. The link between participant information and the study ID is kept in a locked file cabinet, within a locked office, and will only be accessed by study personnel. Coded data is recorded in a database, password protected on a secure server in the Brain Imaging Lab, Psychiatry. Images are transferred to the Brain Imaging Laboratory from the Advanced Imaging Center at DHMC and archived using secure systems. Images and scan readings will become part of each

participant's permanent medical record and this is clearly outlined in the consent form and discussed with each participant during the consent process

d) *Will data that identify individual subjects be published or in any way be disclosed to third parties other than project personnel?*

☐ *Yes* ☒ *No If yes, please explain here and incorporate the information in consent form:*

28. *Responsibility for costs of injury or illness related to research:*

Will the sponsor or other funding agency be responsible for costs of injury or illness related to the research?

☐ *Yes* ☒ *No*

If applicable, describe whether or not the sponsor will be responsible for investigational device removal if required:

NA

If the sponsor or other funding agency will not be responsible for costs of injury or illness related to research, please complete:

a) *The reasons why the sponsor or funding agency is not accepting responsibility for research-related injury.*

NIH does not cover the cost of injury or illness.

b) *Summary of risks as related to potential costs that could be incurred as a result of research-related injury or illness.*

It is possible that a participant could have a severe psychiatric reaction to the drugs used in the study or to the scanning or other study procedures. Should this occur, hospitalization could be required. However, we believe this is extremely unlikely given our pilot work establishing a safe dose of cannabis and dronabinol for this study and since all participants who get study drug will be cannabis users, some schizophrenia patients will be taking antipsychotic medication already, and all will be required to be psychiatrically stable as indicated by outpatient treatment for the past month. If a participant needs psychiatric hospitalization, it will be billed to their insurance.

c) *Describe reasons for requesting that DHMC or Dartmouth College provide coverage for research-related injury or illness, which is not standard policy.*

We are not requesting this.

29. *Participant Remuneration:*

Will participants be paid for their time, reimbursed for travel or meal expenses, or receive any sort of "gift" for participating in this study?

☒ *Yes* ☐ *No*

If yes, please describe in detail:

Note: Participant remuneration is not considered a benefit of being in a research study. CPHS will consider the amount of payment in relation to the time needed and any inconvenience to participants. Payment, reimbursement, or gifts should not be in an amount that would be coercive to the participant population.

If study is to be done at the VA, specific questions need to be answered if a participant is being paid "in excess of reimbursement for travel." Please contact the CPHS office if you need more information.

Participants with schizophrenia will receive a $25 gift card for attending the informational session to learn about the study.

All participants in Groups 1-4 (SCZ-CUD and SCZ only) will be paid:

- $25 for completing the Screening Visit paid as a gift card on the day of the visit
- $50 for the Neuropsych Baseline Visit paid as a check at the end of the study
- $100 for T1 Scan day paid as a check at the end of the study
- $35 will also be "won" on the T1 Test Day for the monetary incentive delay task paid as a check at the end of the study - NOTE: This amount is not disclosed to participants because it would invalidate the testing.
- $200 for T2 Scan day paid as a check at the end of the study
- $35 will also be "won" on the T2 Scan day for the Monetary Incentive Delay task paid as a check at the end of the study
- Participants will "win" between $15-$20 for completing the Probabilistic Reward Task. Over the three sessions, this would not total more than $50. We do not state the exact amount in the consent because it invalidates the testing.

Total = $495: $375 paid as stipends and $120 that is "won"

All participants in Groups 5-7 (CUD only) will be paid:

- $50 for completing the Screening Visit paid as a gift card on the day of the visit
- $50 for the Neuropsych Baseline Visit paid as a check at the end of the study
- $400 for T1 Scan day paid as a check at the end of the study
- $35 will also be "won" on the T1 Test Day for the monetary incentive delay task paid as a check at the end of the study
- $500 for T2 Scan day paid as a check at the end of the study
- $35 will also be "won" on the T2 Scan day for the Monetary Incentive Delay task paid as a check at the end of the study
- Participants will "win" between $15-$20 for completing the Probabilistic Reward Task. Over the three sessions, this would not total more than $50.

Total = $1,120: $1,00 paid as stipends and $120 that is "won"

All participants in Group 8 (Healthy Control) will be paid:

- $50 for completing the Screening Visit paid as a gift card on the day of the visit
- $50 for the Neuropsych Baseline Visit paid as a check at the end of the study
- $200 for T1 Scan day paid as a check at the end of the study
- $35 will also be "won" on the T1 Test Day for the monetary incentive delay task paid as a check at the end of the study
- $200 for T2 Scan day paid as a check at the end of the study
- $35 will also be "won" on the T2 Scan day for the Monetary Incentive Delay task paid as a check at the end of the study
- Participants will "win" between $15-$20 for completing the Probabilistic Reward Task. Over the three sessions, this would not total more than $50.

Total = $620: $500 paid as stipends and $120 that is "won"

In addition, all but Groups 4 and 8 can earn money for being abstinent from alcohol or drugs.

- $90 - A $30 gift card each for confirmed abstinence at Neuropsych Baseline Visit, T1 and T2
- $360 - Participants need to demonstrate two weeks of abstinence prior to the first scan (T1) plus another three visits between T1 and T2. They will go to a local clinic for a visit up to 3 times a week. They will be paid:
    - $10 cash for attending the visit
    - $30 gift card for confirmed abstinence

  We anticipate nine of these visits, though the actual number may fluctuate.

Estimated total for abstinence = $450

The study provides transportation for study visits to participants through a taxi service. This is especially helpful for participants with SCZ who often lack transportation. For those persons who provide their own transportation, the study provides the following reimbursement:

- A $25 gas card for each visit for people coming from 25-49 miles away.
- A $50 gas card for each visit for people coming from 50 miles away or beyond.

IMPORTANT: Participants cannot drive themselves to appointments in which they may receive dronabinol or smoke a marijuana cigarette. They must either have someone else drive or take the taxi provided by the study.

Those participants who choose to have the study provide them with a prepaid cellular telephone will be allowed to keep the cell phone and any unused minutes at the end of the study. The phones will not have a contract.

30. *Use of Drug or Biological Agent:*

Respond to items below or check ☐ *No drug or biological agent involved.*

List the drugs and biologic agents to be used in this study: dronabinol, marijuana

Is each drug or biological agent approved by the FDA for the specific indication for which it is used in this study?

Drug or Biologic Agent: dronabinol ☐ *Yes* ☒ *No*

Drug or Biologic Agent: marijuana ☐ *Yes* ☒ *No*

If no, respond to a and b for each drug or biologic agent used for an unapproved indication:

a) *Briefly discuss the plan for the storage, dispensing, handling, and disposal of investigational and FDA-approved drugs, devices, and biologics. When these activities are being done by the investigator, include a description of the procedures for inventory control and documentation.*

DHMC Investigational Pharmacy is managing all study drugs.

☒ *Yes* ☐ *No* *If No please describe management plan below.*

b) *Check and respond to one of the following statements for each drug or biologic agent:*

☒ *If this study is being done under an Investigational New Drug (IND) application to the FDA please provide: IND # (Investigational New Drug): #* 106130 *and specify who holds the IND#:* Mary F Brunette, MDOR

☐ *If a drug or biologic agent or the combination of drugs or agents is not FDA approved for the indication for which it is used in this study, but an IND # has not been obtained, please* ***complete Attachment J.***

31. *Placebo vs. Standard Care:*

Does any part of the study involve use of a placebo or procedures that are inconsistent with the standard of care at DHMC?

☒ *Yes* ☐ *No* *If yes, respond to* ***Placebo: Attachment B***

32. *Medical Device:*

Respond to items below or check ☒ *No devices involved.*

List the devices to be used in this study:

Is each device approved by the FDA for this indication?

Device: _____ ☐ *Yes* ☐ *No*

Device: _____ ☐ *Yes* ☐ *No*

If no or if FDA approval is pending, respond to a, b, and c for each device used for an unapproved indication.

a) *Is the device provided free of charge by the sponsor?*

☐ *Yes* ☐ *No*

b) *Where are the devices used in the study stored? Who controls their use?*

c) *Respond to (1), (2), (3), or (4)*

(1) *If this study is being done under an Investigational Device Exemption (IDE) from the FDA please provide: IDE#: #___ or check here if the IDE is pending:* ☐

Also check the FDA Device HCFA Reimbursement Category:

☐ *A* ☐ *B2* ☐ *B3*

Please note: CPHS will not approve a study before an IDE # has been received. OR

(2) *If 510(k) notification for a device has been sent to FDA check here* ☐ *and either: provide a copy of the documentation verifying 510(k) clearance, or check here if 510(k) clearance is pending* ☐*. OR*

(3) *If a device is exempt from IDE requirements, check here* ☐ *and provide a copy of a letter from the FDA or sponsor stating that the device is exempt from IDE requirements under 812.2(c). OR*

(4) *If you are requesting a* ***nonsignificant risk*** *determination for a device from CPHS, please check here* ☐ *and complete* ***Attachment A***.

Please note: The CPHS may approve, disapprove, or require modifications in a protocol that has been approved or cleared by the FDA.

33. *Conflict of Interest Review:*

Dartmouth College, Dartmouth-Hitchcock Clinic, Mary Hitchcock Memorial Hospital, and the Hitchcock Foundation have adopted a policy on Conflict of Interest that applies to each study reviewed by the CPHS. Copies of the policy are available on the CPHS web site at http://www.dartmouth.edu/~cphs/policies/.

Instructions: *To assist institutional review of the proposed research for conflicts of interest, please respond to the questions below as applicable to this study. Definitions of terms are available at the end of this section.*

Regarding only this proposed research study, does any investigator or other individual among the research staff, including certain family members, hold a financial or other outside interest that would reasonably appear to affect or be affected by the proposed study that:

a. Consists only of compensation for services or equity in a publicly held entity worth less than $5000 when combined in the prior 12 months or anticipated during the next 12 months?

☒ No or not applicable. *Please answer the next question.*
☐ Yes. *Please add an appropriate disclosure to the "Funding" section of the consent form for this study.*

b. Consists of i) compensation for services or equity in publicly held company worth $5000 or more when combined in the prior 12 months or anticipated during the next 12 months, ***or*** ii) any equity in a privately held entity, iii) intellectual property rights, or iv) another outside interest, which may present a conflict? The latter interests listed here are limited to those held or received over the prior 12 months and those anticipated in the next 12 months.

☐ No or not applicable.
☒ Yes. *Please follow the instructions below.*

c. Consists of reimbursed or sponsored travel from a single entity worth $5000 or more that was received over the prior 12 months and is anticipated in the next 12 months?

☒ No or not applicable.
☐ Yes. *Please follow the instructions below.*

*If you have answered "**No**" to the three questions above, no further information or action is needed.*
*If you have answered "**Yes**" to question #33b or #33c, then please identify each individual holding the outside interest*

Robert M. Roth, PhD is an author of the BRIEF-A, a questionnaire measure that will be used in the project. He receives royalties from the publisher who holds the copyright (Psychological Assessment Resources, Inc; PAR, Inc). Dr. Roth will provide the BRIEF-A gratis to the project from the copies he receives for free for research annually from the publisher.

***Each individual listed above** should complete a CPHS Conflict of Interest Disclosure Form. The **CPHS Conflict of Interest Disclosure Form** is available on the CPHS website at the following url:*
http://www.dartmouth.edu/~cphs/tosubmit/forms/

Please send an electronic copy of the completed disclosure form to CPHS.Tasks@dartmouth.edu *or a paper copy to the CPHS office at Hinman box #6254. These copies should be clearly identified as containing confidential information.*

Definitions:
"**Conflict of interest**" occurs when an individual's outside interests, financial or otherwise, might reasonably lead an independent observer to question whether the individual's actions or decisions in connection with a study are influenced by the outside interests.
Conflicting interests do **not** include:

- Salary from Dartmouth College, Dartmouth-Hitchcock Clinic, Mary Hitchcock Memorial Hospital, and the Hitchcock Foundation or income from consulting done on behalf of one of these entities;

- Income from seminars, lectures, teaching engagements, or service on advisory committees or review panels sponsored by:
  - A federal, state, or local governmental agency,
  - A U.S. institution of higher education,
  - An academic teaching hospital,
  - A medical center, or
  - A research institute that is affiliated with a U.S. institution of higher education;
  - Income from mutual funds or other retirement accounts where the holder does not directly control the investment decisions;
  - Copyrights in books, primary literature, or presentations. This exclusion does not apply to income resulting from such copyrights.

"**Investigator or research staff**" means the project director or principal investigator and any other person, including a student, research support staff member, consultant, or collaborator who is responsible for the design, conduct, or reporting of research involving human subjects. For the purposes of conflict of interest review, this term includes spouses, domestic partners, and dependent children of investigators and research staff.

"**Publicly held entity**" means a company that has stock publicly traded on a stock exchange.

Attachment B
Placebo or Procedures that are Inconsistent with the Standard of Care

Consider the ethical implications of using a placebo or procedures that are inconsistent with the standard of care in this study. Specifically, explain what "standard of care" therapy is for this participant population and how the use of placebo therapy may affect risks for participants. Also discuss:
a) the safety and efficacy of other available therapies (if any),
b) the maximum total length of time a participant may receive placebo on study,
c) the greatest potential harm that may come to a participant as a result of not receiving effective therapy (immediate or delayed onset), and
d) safeguards for the participants receiving placebo.

Required comment from the local research team specifically addressing a-d above and in addition to any justification included in the study protocol. Information copied directly from the protocol is not acceptable in this section:

Placebo is being used in this study, but not as a treatment, because this is not a treatment study. All individuals in this study, who are diagnosed with schizophrenia, are in active treatment for their symptoms throughout the study. Placebo is given to those participants with SCZ-CUD and those with CUD only on a single occasion to maintain the blinding of the study and to serve as a control condition. Participants are to receive one of the following:

- Two 7.5mg dronabinol capsules and a placebo marijuana cigarette
- Placebo capsules and an active marijuana cigarette
- Placebo capsules and a placebo marijuana cigarette

a) Safety and efficacy of other therapies – The placebo is not being used to replace another therapy, therefore this question does not apply.
b) Maximum amount of time a participant may receive placebo – One day
c) Greatest potential harm from not receiving treatment – This does not apply because this is not a treatment study. All SCZ-CUD participants are receiving treatment during the study. CUD only participants are not receiving treatment, but they have not been receiving any treatment and are not seeking treatment.
d) Safeguards for persons receiving placebo – This question does not apply. While there are a multitude of safeguards, they are in place to protect people from the potential harms from receiving dronabinol or marijuana.

Attachment C
Genetic Research

For research studies involving genetic testing the CPHS describes below two categories of studies to assist its further review. The researcher should determine if the research falls into category A or B as described below. If the research falls into category A. indicate by checking below and add comments as appropriate to this research project.
If the research falls into category B. please respond to questions that follow.

Respond to A or B:

☒ *A. The study is looking for an association between a genotype or a biomarker and a specific disease or condition, but at this point it is not clear if the genetic marker has predictive value. The uncertainty regarding the predictive value of the genetic marker is such that studies in this category will not involve referral of participants to genetic counseling.*

Comment:

Participants will have the option of donating a genetics sample for analysis to explore the relation of genetic markers to brain function and structure. Participants will also have the option to have their blood and/or genetics specimen banked for future research. Because this genetics research is exploratory and will not likely provide a meaningful result for individual participants, they will not be given the results of the genetic testing. If new information develops during the study such that results of the analysis would be meaningful to participants, then we would approach the IRB at that time to discuss the proper course of action. Additional information is provided on page 15 of the Study Plan.

☐ *B. The study is based on the premise that a link between a genotype or a biomarker and a specific disease or condition is clinically useful in predicting the development of that specific disease or condition.*

Respond to the items below:
1. Are clear guidelines established for disclosure of information, including interim or inconclusive research results, to the participants?

2. Will participants be told what genetic information (and its meaning) they may receive at a certain point in the research?

3. Will family members be protected against disclosure of medical or other personal information about themselves to other family members?

4. Will participants be given the option not to receive information?

5. Will limits on protections be clearly communicated to participants, including advance consent to disclosures about health risks to family members?

6. Are the possible psychological and social risks of genetic research included in the consent process?

7. Will genetic counseling be provided, both as part of the consent process and when communicating test or other research results to participants?

8. Will participants be informed about the possibility of important incidental genetic findings such as paternity and heritable conditions other than the one(s) under the study?

9. Will the study data be protected from disclosure to third parties, such as employers and insurance companies? How?

10. Will participants be informed about the potential consequences of a third party, such as employer or insurance company, becoming aware of the study findings?

11. Will the data be stored in a secure manner? How?

12. Will the data be coded? Who holds the key to the code?

13. Is a request for a certificate of confidentiality necessary?
☐*Yes* ☐*No* *If No, why not?*

14. Does the investigator plan to disclose research findings to participants or their physicians for clinical use? Describe the clinical significance of the findings to participants.

15. Is the possibility of disclosure of study findings to participants discussed during the consent process with prospective participants?

16. How will the biospecimens be stored?

17. Will biospecimens be made available for future use by participants? by other investigators? for new studies?

18. What will happen to data and biospecimens in the event of withdrawal from the study?

19. How will the privacy of participants be protected when study results are published?

20. If research involves family members:
20a. How will family members be recruited for study participation?
20b. Will information be obtained from the medical records of family members?

In general, the consent process and form should include the following information:
- they will receive only the genetic information the investigator feels is clinically significant and reliable, or no genetic information will be provided;
- at what point in the study they will receive genetic information;
- they may find out things about themselves or their family that they did not really want to know, or that they may be uncomfortable knowing;
- information about themselves may be learned by others in their family;
- any effect on their insurability;

- actions taken as a result of participation may expose participants to risks (e.g. submitting insurance claim forms for the costs of genetic counseling);
- available protections for the confidentiality of study data;
- what the consequences of withdrawal from the study are; and
- costs to them that may be associated with participation (including, for example, the cost of genetic or psychological counseling).

Attachment D
Employees and Students

One of the primary responsibilities of the CPHS is to ensure that a participant's decision to participate in research will be voluntary and that consent will be sought "only under circumstances that provide the prospective subject... sufficient opportunity to consider whether to participate and that minimize the possibility of coercion or undue influence." Students and employees may be vulnerable to "subtle inducements to participate".

The researcher who plans to recruit either population must ***define clearly the participants to be enrolled and the rationale for their participation****. In addition, the mode and timing of recruitment must be explained.*

Another special consideration for employee and student populations is the issue of confidentiality of research data. Depending on the nature of the research and the data collected, a break of confidentiality could affect a person's employment, career path, educational plans, or social relationship with the hospital/academic community. Therefore, the researcher should ***document carefully the methods to protect the subjects' identity and research data*** *(e.g., coding, storage of research files, limits of accessibility to research data, etc.).*

Comment:

We are not specifically recruiting employees or students of Dartmouth College, Geisel School of Medicine or DHMC, but anticipate that some people who are employees and/or students will respond to advertisements for this study and if appropraite will be entered into the study. Because of the nature of this study, there are already a fairly large number of precautions in place to protect the privacy of individuals. These would also apply to students and employees. The specifics of this and the limits are clearly spelled out in both the study plan and consent form.

Please Note: Studies enrolling Dartmouth Medical School students must be reviewed by the Medical Education Institutional Review Committee (MEIRC).
☐ *Check here if you plan to enroll Dartmouth Medical School Students.*
Contact Greg Ogrinc MD for more information about MEIRC review.

Attachment E
Illiterate Subjects

Subjects who are unable to read should not be excluded from research on the grounds of illiteracy. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written consent form and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial, and, if capable of doing so, has signed and personally dated the consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

Comment:

We do not anticipate recruiting Illiterate participants, but cannot rule it out. If this occurs, we will follow the above guidance.

Attachment G
Research Involving Individuals With Impaired Decision-Making Capacity

Introductory Information:

*When a subject lacks capacity to give informed consent, the investigator should obtain written permission from a **legally authorized representative** prior to enrolling the subject in a research study. Federal Regulations define **legally authorized representative** as an "individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research" (45CFR46.102(c)). Neither Federal Regulations nor New Hampshire State Law provide specific information about who may or may not qualify as a **legally authorized representative** in a research setting. For the purposes of this policy statement, the options of defining a legally authorized representative include:*

a) Durable power of attorney for health care (DPAHC),
b) Court appointed legal guardian
c) Next-of-kin.

A strict interpretation of NH state law does not provide for the use of next-of-kin as a surrogate decision maker for investigational activity. The argument for allowing next-of-kin to consent to participation in research activity for an individual who lacks capacity to consent is that, without such an option, it is often impractical or impossible to conduct important medical research on conditions where results with the best current therapy are suboptimal. When investigational therapy represents the best treatment option or when risks to the subject are small in relation to the potential benefit of research to society, a policy which creates a major obstacle to the conduct of important research activity is ethically unsound.

*With the above issues in mind, the Dartmouth CPHS has established the following policy for research studies that may involve adult subjects who lack capacity to give informed consent to participation in a research study. **Please carefully review all items.***

Submission requirements:

When initially submitting a protocol for review by the CPHS, the investigator will inform the CPHS in the appropriate section of the CPHS Study Plan (item #18) if the study may involve subjects who lack capacity to give informed consent to participate in the study being proposed.

In addition, when a study may involve subjects who lack capacity to give informed consent, the investigator will use the form provided below to inform the CPHS of the requested options to provide permission for an individual who lacks capacity to participate in the research study and respond to specific CPHS questions.

For all requests:

Even with the permission of a DPAHC, or court appointed legal guardian, the CPHS will not permit a subject who lacks capacity to give informed consent to participate in a research study that offers little chance of DIRECT BENEFIT to the research subject over what they could receive outside the research setting and involves a meaningful increase in the risk of harm or discomfort, regardless of the potential gain to future subjects or society in general.

Please complete a) and b):

a) *Does participating in this study offer the subject a chance of direct benefit over what they could receive outside the research setting?*

We will allow individuals with legal guardians who meet eligibility criteria for Groups 1-3 - Participants with SCZ-CUD and Group 4 - Control participants with SCZ to participate in this study. Persons who have a legal guardian but do not have schizophrenia (Groups 5-8) would not qualify for this study.

For persons in the SCZ-CUD group, there is a direct benefit because there is really no place from which they could receive the contingency management program that is used to help people to abstain while in this study. For control participants with SCZ (but not CUD), there is no direct benefit.

b) *Is there an increase in the risk of harm or discomfort for the subject over what they would experience outside the research setting?*

No - The MRI, blood draws and other testing are routine non-invasive medical procedures that many people experience. Participants in the SCZ-CUD group may be exposed to THC through a capsule or by smoking it on a single instance, but persons meeting the criteria for these groups take this (through marijauana use) on their own on a regular basis.

When there is a meaningful chance of DIRECT BENEFIT to the research subject over what they could receive outside the research setting, the CPHS will make a judgment decision about who may consent to participation in the study. The options include: DPAHC, court appointed legal guardian, and a properly motivated next-of-kin.

Please indicate the option(s) requested to allow for consent if a subject is incompetent to provide consent:

Durable power of attorney for health care (DPAHC)	☐ *YES*	☒ *NO*
Court appointed legal guardian	☒ *YES*	☐ *NO*
Next-of-kin.	☐ *YES*	☒ *NO*

<u>If a study requests the use of Next-of-Kin as the legally authorized representative, Please complete a) through e) below:</u>

a) Could the subject receive the same management that they will receive in the research study outside the setting of a research protocol?

b) Will participation in the study increase the risk of harm or discomfort compared to what is expected with the management that the subject will receive if they do not participate in the research study?

c) Will participating in the study increase the chance that the subject will experience a favorable outcome compared to what is expected with the management that the subject will receive if they do not participate in the research study?

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d) What is the magnitude of the benefit that future patients, or society in general, may experience as a result of the subject participating in this study?

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e) The process of appointing a legal guardian may take several months. Would this type of delay compromise patient care?

The CPHS will use the responses to the items a) – e) when discussing the option of allowing Next-of-Kin to enroll subjects into a research study.

Signature section of the consent form:

Below is the signature line to use when individuals lacking decision-making capacity may be enrolled into a research study. As described above, use of the next-of-kin option requires special CPHS approval:

Participant Signature and Date *Printed Name*

If participant lacks capacity to provide informed consent, sign below as appropriate:

Durable Power of Attorney for Health Care and Date *Printed Name*

or

Court Appointed Legal Guardian and Date *Printed Name*

or

Next-of-kin and Date *Printed Name*

Decision by the CPHS:

The CPHS decision will be relayed to the investigator via the CPHS approval letter.